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Attorney's Docket No.: 06275-188001 / D 1576-1P US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Tommy Ekstrom
Serial No. : 09/367,950
Filed : August 18, 1999
Title : NEW USE

Art Unit : 1617
Examiner : Jennifer M. Kim

Mail Stop Appeal Brief - Patents
Commissioner for Patents
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BRIEF ON APPEAL

Appellant is appealing the final rejection of claims 13-36, 38, 42, and 43 in the Office Action dated September 21, 2005, and the Advisory Action dated December 14, 2005. A Notice of Appeal was filed and received by the U.S. Patent and Trademark Office on January 5, 2006.

(i) Real Party in Interest

The Real Party in Interest is AstraZeneca AB, the assignee of record, which is a subsidiary of AstraZeneca PLC.

(ii) Related Appeals and Interferences

There are no prior or pending related appeals, judicial proceedings, or interferences.

(iii) Status of Claims

Claims 1-12, 37, and 39-41 are canceled.

Claims 13-36, 38, 42, and 43 are rejected and under appeal.

(iv) Status of Amendments

The Advisory Action dated December 14, 2005, states that, for purposes of appeal, all previously filed amendments have been entered. No amendments are being submitted herewith.

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(v) Summary of Claimed Subject Matter

The claims are directed to methods of prevention and treatment of asthma symptoms and to methods of reducing the incidence of acute asthma attacks. Claims 13, 35, 36, 42, and 43 are the independent claims.

Independent claim 13 is directed to methods of prevention and treatment of asthma symptoms, which include instructing a patient to inhale an effective amount of a composition including, in admixture, (a) a first active ingredient which is formoterol, a pharmaceutically acceptable salt or solvate thereof or a solvate of such a salt, and (b) a second active ingredient which is budesonide. The patient is instructed to inhale the composition on demand, as determined by the patient based on the patient's symptoms, as a treatment and a preventative measure, when the patient experiences an increase in asthma symptoms. Support for independent claim 13 can be found in the specification, *e.g.*, at page 2, lines 22-28; and page 4, lines 4-23.

Independent claim 35 is directed to methods of prevention and treatment of asthma symptoms, which include instructing a patient to inhale an effective amount of a composition including, in admixture, (a) a first active ingredient which is formoterol, a pharmaceutically acceptable salt or solvate thereof or a solvate of such a salt, and (b) a second active ingredient which is budesonide. The patient is instructed to inhale the composition on demand, as determined by the patient based on the patient's symptoms, as a complement to maintenance treatment of the patient's asthma. Support for independent claim 35 can be found in the specification, *e.g.*, at page 2, lines 22-28; page 4, lines 8-23; and page 8, lines 24-29.

Independent claim 36 is directed to methods of prevention and treatment of asthma symptoms, which include instructing a patient to inhale an effective amount of a composition including, in admixture, (a) a first active ingredient which is formoterol, a pharmaceutically acceptable salt or solvate thereof or a solvate of such a salt, and (b) a second active ingredient which is budesonide. The patient is instructed to inhale the composition on demand, as determined by the patient, when the patient is expecting to encounter an asthma triggering event, as a preventative measure. Support for independent claim 36 can be found in the specification, *e.g.*, at page 2, lines 22-28; page 3, lines 7-9 and 18-19; and page 4, lines 8-10 and 19-23.

Independent claim 42 is directed to methods of prevention and treatment of asthma symptoms, which include instructing a patient to inhale an effective amount of a composition including, in admixture, (a) a first active ingredient which is formoterol, a pharmaceutically acceptable salt or solvate thereof or a solvate of such a salt, and (b) a second active ingredient which is budesonide. The patient is instructed to take a maintenance dose of the composition, and, if the patient experiences asthma symptoms, to inhale additional doses as needed to improve control and provide acute relief. Support for independent claim 42 can be found in the specification, *e.g.*, at page 2, lines 22-28; page 4, lines 8-12 and 19-23; and page 8, lines 24-29.

Independent claim 43 is directed to methods of reducing the incidence of acute asthma attacks, which include instructing a patient to inhale an effective amount of a composition including, in admixture, (a) a first active ingredient which is formoterol, a pharmaceutically acceptable salt or solvate thereof or a solvate of such a salt, and (b) a second active ingredient which is budesonide. The patient is instructed to inhale the composition on demand, as determined by the patient based on the patient's symptoms, as a treatment and to reduce the incidence of acute asthma attacks, when the patient experiences an increase in asthma symptoms. Support for independent claim 43 can be found in the specification, *e.g.*, at page 2, lines 22-28; page 3, lines 21-27; page 4, lines 8-12; and page 8, lines 24-29.

(vi) Grounds of Rejection to be Reviewed on Appeal

Claims 13, 35, 36, and 42 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement.

Claims 13-15, 17, 18, 20-36, 38, 42 and 43 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentably obvious over Carling *et al.* (WO 93/11773).

Claims 16 and 19 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentably obvious over Carling *et al.* and further in view of Aberg *et al.* (U.S. Patent No. 5,795,564) and Ryrfeldt *et al.* (*Biochem Pharmacol.* 38:17-22, 1989, Abstract).

(vii) Argument

I. Rejection under the enablement requirement of 35 U.S.C. § 112, first paragraph.

Claims 13, 35, 36 and 42, stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. The enablement requirement mandates that the specification describe how to make and how to use the invention. MPEP 2164. The four rejected claims are drawn to methods of prevention and treatment of asthma symptoms, each claimed method comprising a step of instructing a patient to inhale an effective amount of a composition containing the defined active ingredients. The rejected claims differ in the details of the instructions to the patient, details that are not pertinent to this particular ground for rejection. Rather, the Examiner has focused on the claim term "prevention".

In the final Office Action dated September 21, 2005 ("the final Office Action"), the Examiner stated that "the specification, while being enabling for the treatment of an acute episode of asthma, does not reasonably provide enablement for the 'prevention of an acute episode of asthma.'" Final Office Action at page 3. Thus, the Examiner acknowledges that the enablement requirement is met for the "treatment" aspect of the claimed methods, and challenges only the "prevention" aspect.

The standard for enablement is whether any experimentation needed to practice the invention is undue. In re Wands, 858 F.2d 731, 737 (Fed. Cir. 1988). See also United States v. Telectronics, Inc., 857 F.2d 778, 785 (Fed. Circ. 1988), which states that "[t]he test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation." In Wands, the Federal Circuit set forth the criteria for determining whether the amount of experimentation is undue. These criteria include: i) quantity of experimentation necessary, ii) amount of direction or guidance presented, iii) presence or absence of working examples, iv) nature of the invention, v) state of prior art, vi) relevant skill of those in the art, vii) predictability or unpredictability of the art, and viii) breadth of the claims. In re Wands, 858 F.2d at 737.

The final Office Action includes at pages 3-6 the Examiner's views of how the various Wands factors should be applied to the "prevention" aspect of the present claims, the aspect that

she believes is not enabled. Appellant addresses the Examiner's views of each of these factors in the order in which they appear in the final Office Action.

Nature of the Invention: The final Office Action says at page 3, "The nature of the invention is extremely complex in that it encompasses the actual prevention of an acute episode of asthma such that the subject treated with above composition does not contract an acute episode of asthma." No explanation is offered as to why this is deemed to be "extremely complex." The Examiner simply deems it so.

In fact, preventing acute episodes of asthma by the methods of the invention is quite simple. As explained in the specification at page 3, lines 7-19,

> Acute asthma attacks may occur on an irregular basis when exposed to an agent e.g. during the pollen season, a virus infection, cold air, perfumes or any other agent(s) triggering an asthma attack in the patient...We contemplate preventive use when the patient expects to encounter asthma inducing conditions e.g. intends to take exercise or go into smoky conditions.

This "preventive use" is accomplished by simply using the formoterol/budesonide composition that is taught throughout the specification (the same composition as for treatment), delivered via inhalation in the manner that is taught throughout the specification (the same delivery method as for treatment), but where the timing of the administration is at a point before the symptoms of an acute attack begin, or early in the development of an acute attack when the symptoms are still relatively minor but are felt by the patient. When a patient knows in advance that he/she is about to encounter asthma-triggering conditions such as those mentioned in the specification, he/she can take preventative action by using the formoterol/budesonide inhaler in accordance with the claimed methods, i.e., "on demand" or "as needed." Alternatively, once the patient realizes that his/her symptoms are developing and may lead to a full asthma attack, he/she can take preventative action by using the inhaler in accordance with the claimed methods to prevent development of the full asthma attack. Why the Examiner continues to believe this is at all "complex" is a mystery to Appellant.

Breadth of the claims: The final Office Action says at page 4:

> The complex of nature of the claims Greatly exacerbated by breath of the claims. The claims encompass prevention of a complex cell autoimmune disorder in humans which has potentially many different causes (i.e. many different allergen or combination of allergens). Each of which may or may not be addressed by the administration of the claimed composition. (Non-standard English in the original)

Appellant notes that, regardless of the agent that triggers an asthma attack in a given patient, all such attacks appear to involve (1) inflammation of the airways, and (2) bronchoconstriction. Appellant theorized that administering an anti-inflammatory agent (budesonide) simultaneously with a bronchodilating agent (formoterol) prior to onset of such symptoms would prevent the symptoms from occurring; further, the increased use of the claimed combination during a period such as pollen season would effectively ensure sufficient budesonide is administered to protect the patient from exacerbations even at night during this especially risky period. This is discussed in the specification at page 4, lines 19-23. The particular allergen or other asthma trigger is irrelevant to the claimed invention. Thus, the breadth of the claims is perfectly in line with the enablement provided in the specification.

Guidance in the Specification: The final Office Action states at page 4,

> The guidance given by the specification as to how one would administer the claimed composition to a subject in order to actually prevent an acute episode of asthma is minimal. All of the guidance provided by the specification is directed towards treatment rather than prevention of an acute episode of asthma.

This is simply not true, as has been pointed out repeatedly to the Examiner during prosecution. The specification makes it clear that the guidance in the specification about formulations, dosage, delivery, etc. applies to both prevention and treatment. See, for example, the specification at page 1, lines 11-15:

> The invention further relates to a method for prevention or treatment of an acute condition of asthma and/or intermittent asthma and/or episodes in chronic asthma by administering, by inhalation, a composition comprising the first and second active ingredients as defined previously. (emphasis added)

This description of the method as including both prevention and treatment is reiterated at page 3, lines 21-27, where the composition is more explicitly described as containing (a) formoterol, a pharmaceutically acceptable salt or solvate thereof or a solvate of such a salt; and (b)

budesonide. In addition, the text quoted above from page 3, lines 7-19, concerning how preventive use would be accomplished, is also very relevant to this Wands factor. As indicated above, the patient would administer the composition when he/she expects to encounter asthma-triggering conditions, such as pollen season, cold air, exercise, or smoke.

The specification also provides on pages 5-9 detailed teachings regarding formulations, ratios of the active ingredients, doses, types of inhalers, etc., all of which apply equally to use for prevention or treatment. The Examiner's view that "[all] of the guidance provided by the specification is directed towards treatment rather than prevention of an acute episode of asthma" is therefore unsupported by the facts.

Working Examples: The final Office Action states at page 4: "All of the working examples provided by the specification are directed toward the treatment rather than prevention of an acute episode of asthma." Appellant is unsure of how the Examiner has arrived at this conclusion. There are six working examples in the specification, on pages 7-9. The first four describe preparation of various formoterol/budesonide formulations and filling them into inhaler devices. There is no indication in any of these examples that they concern formulations useful only for treatment, and not prevention, of acute episodes of asthma. In fact, as discussed above, the specification makes it clear that the same compositions are useful for both prevention and treatment. Examples 5 and 6 are prophetic descriptions of how a patient can use the formoterol/budesonide composition in various ways. Though neither description mentions "prevention" per se, the uses described can be read as encompassing preventive use. For example, the patient with "intermittent asthma" (e.g., asthma triggered by exercise or specific allergens) of Example 6 uses the combination "as needed until the asthma resolves." Given the disclosure elsewhere in the specification that the patient can administer the combination prior to encountering conditions that trigger his/her asthma, the prophetic description in Example 6 clearly includes use prior to the triggering event or early in the process before the symptoms have become severe: *i.e.*, preventive use. Appellant sees no justification for reading it as exclusively limited to treatment that begins only after the patient is in the throes of a full-blown attack. Accordingly, most if not all of the working examples appear to be equally applicable to both treatment and prevention.

Furthermore, working examples are not even required to satisfy the enablement requirement. As stated by the U.S. Court of Customs and Patent Appeals, "a specification need not contain a working example if the invention is otherwise disclosed in such a manner that one skilled in the art will be able to practice it without an undue amount of experimentation." In re Borkowski, 422 F.2d 904 (CCPA 1970).

State of the Art: The final Office Action says at pages 4-5:

> While the state of the art is relatively high with regard to treatment of an acute episode (i.e. acute asthmatic attack), the state of the art with regard to prevention of such disorders is underdeveloped. In particular, there do not appear to be any examples or teachings in the prior art wherein a composition similar to the claimed compounds was administered to a subject to prevent development of an acute episode of asthma. (emphasis in original)

Appellant first points out that any lack of examples in the art goes to the novelty and nonobviousness of the claimed invention, rather than lack of enablement. "The mere fact that something has not been previously done clearly is not, in itself, a sufficient basis for rejecting all applications purporting to disclose how to do it." In re Chilowsky, 229 F.2d 457, 461 (CCPA 1956). That said, the art is not completely bereft of examples of compositions that can be used to prevent development of asthma symptoms into an acute attack, as the Examiner maintains. In fact, so-called "maintenance therapy" with anti-inflammatory glucocorticosteroids, a well-known concept at the priority date of the present application, is for the purpose of controlling inflammation over the long term, and thereby reduce the number of asthma attacks suffered by the patient. Appellant submitted evidence in this regard with the Amendment filed June 29, 2005, in response to the Office Action of March 30, 2005. A copy of that evidence, the PULMICORT® TURBUHALER® budesonide inhalation powder inhaler product insert (dated June 1997), is included as Exhibit A in the Evidence Appendix attached to this brief. On page 2 of the insert is a section entitled "Patient's Instructions for Use." For ease of reference, Appellant has marked a part of this section that tells the patient, "**Pulmicort Turbuhaler works to prevent and reduce your asthma symptoms and attacks.**" (Exhibit A, page 2, circled section marked "H"; emphasis added.) While this product insert does not concern a product having the precise combination of active ingredients required by the present claims, and does not

suggest that budesonide can be used "on demand" or "as needed", as required by the present claims, it does illustrate that the general concept of "prevention" of asthma attacks was well known in the art before the present application's priority date. Appellant therefore does not understand the Examiner's statement (quoted above from the final Office Action) that "there do not appear to be any examples or teachings in the prior art wherein a composition similar to the claimed compounds was administered to a subject to prevent development of an acute episode of asthma." In fact, Appellant had already provided to the Examiner just such "examples or teachings in the prior art" in Appellant's June 29, 2005, submission.

See also the various internet publications included in the Evidence Appendix as Exhibit F. These three pages were printed out by Appellant's representative on June 23, 2005, and submitted with the June 29, 2005, amendment referred to above. While not prior art, they do help illustrate that those of skill in the field of asthma drugs utilize the term "prevent" in the context of asthma attacks (see circled text on each page). The first describes budesonide as a drug "used to **prevent** asthma attacks." The second says that "Regular use of budesonide inhalation powder will help **prevent** asthma attacks." The third says, "Budesonide inhalation will not stop an asthma attack that has already started. It is used to **prevent** attacks." These were a few of the ones found by a simple GOOGLE™ search for internet sites with the terms "prevent", "asthma" and "budesonide" (27,800 hits found in 0.1 sec). They illustrate that those in the art understand that acute episodes of asthma can indeed be "prevented" with appropriate use of asthma drugs. That this was true (and was firmly recognized in the art) back at the time the present application was filed is established by the evidence in the 1997 product insert that is Exhibit A. There is therefore no rational basis for taking the position that those in the art would have believed "prevention" of an acute episode of asthma is "underdeveloped" (the Examiner's word) or unknown in the art.

Predictability of the Art: The final Office Action states at page 5,

> The lack of significant guidance from the specification or prior art with regard to the actual prevention of an acute episode of asthma in a human subject with the claimed compounds makes practicing the claimed invention unpredictable in terms of prevention of an acute episode of asthma. (emphasis in original)

Since the quoted statement does not take into account either the fact that there is indeed significant guidance from the specification (as elaborated above) or the understanding in the art that "prevention" is not an impossible concept in the field of asthma medications (also as elaborated above), there is no logical basis for the assertion embodied therein. Furthermore, contrary to all of the Examiner's concerns, the claimed methods actually do work as predicted in the specification. See the clinical study published by O'Byrne *et al.* ("Budesonide/Formoterol Combination Therapy as Both Maintenance and Reliever Medication in Asthma," Am J Respir Crit Care Med 171:129-136 (2005)) that was made of record in this case with the Amendment filed June 29, 2005. A copy of that publication is included in the Evidence Appendix as Exhibit D. O'Byrne *et al.* compared the outcomes in asthma patients instructed to use one of three different protocols, the first of which is generally in accordance with the presently claimed methods:

(1) **a combination budesonide/formoterol composition, prescribed for use twice a day PLUS additional doses of the same composition "as needed" (i.e., as determined by the patient), referred to as the "bud/form maintenance + relief" group**;

(2) combination budesonide/formoterol composition just twice per day, plus a different drug, terbutaline, as needed (a standard form of therapy that is not within the present claims); and

(3) budesonide alone just twice per day, plus terbutaline as needed (another standard form of therapy that is not within the present claims).
(See "Study Design" in the first column of page 130.)

Of the results reported by O'Byrne *et al.*, perhaps the most relevant to the present enablement issue regarding "prevention" are shown in the first bar graph of Figure 1B on page 132. This graph shows the total number of severe asthma exacerbations experienced by the patients in each treatment group. (An "exacerbation" is an acute asthma attack.) The bud/form maintenance + relief group (i.e., those treated in accordance with the presently claimed methods) experienced dramatically fewer severe exacerbations than either of the other treatment groups—reduced by almost half! This, of course, means that nearly half of the severe exacerbations the patients

would have experienced while being treated by one of the other accepted therapies were *prevented* by instructing the patient to use the budesonide/formoterol composition both as regular maintenance therapy twice per day **and also "as needed".** Treatment group (2) used the budesonide/formoterol composition solely as twice-per-day maintenance therapy, and experienced far worse results, demonstrating that it was not this shared "maintenance therapy" aspect that produced the benefits in the bud/form maintenance + relief group.

As further evidence that the present claimed methods can prevent asthma attacks, Table 2 on page 133 of O'Byrne *et al.* reports that both severe and mild exacerbations were decreased in the bud/form maintenance + relief group, compared to the other groups, demonstrating again a *prevention* of many of exacerbations that would otherwise have occurred in this group. This group showed better results in many other measures as well. (Note that no untreated control group was included in the study, so the reported results necessarily underestimate the beneficial effects of the presently claimed methods compared to no therapy at all. In other words, the ability of the claimed methods to *prevent* acute asthma attacks is in all likelihood even better than the numbers in O'Byrne indicate.)

The formulations and dosage of budesonide and formoterol used in this study (80 μg budesonide/4.5 μg formoterol twice a day plus more "as needed", delivered in a Turbuhaler® dry powder inhaler device) are in accordance with the teachings of Appellant's specification. See, e.g., the specification at page 5, lines 19-30; page 6, lines 19-20, and page 8, lines 24-29. This is definitive evidence that Appellant's claimed methods of prevention and treatment work as predicted in the specification, and required no experimentation beyond the guidance provided in the specification in order to make them work.

The Amount of Experimentation Necessary: The final Office Action says at page 5,

> In order to practice claimed invention, one of skilled in the art would have to first envision a combination of appropriate pharmaceutical carrier, compound dosage, duration of treatment, route of administration, etc. and appropriate animal model system for one of the claimed compounds and test the combination in the model system to determine whether or not the combination is effective for prevention of an acute episode of asthma. (Emphasis and non-standard English in the original)

The final Office Action goes on to describe round after round of experimentation that the Examiner supposes would be necessary, concluding that it would require "undue, unpredictable experimentation to practice the claimed invention to prevent the development of an acute episode of asthma in a subject by administration of the claimed composition."

All of this is quite puzzling. Appellant's specification taught exactly what to do. The two active ingredients (budesonide and formoterol) and the route of administration (inhalation) are precisely defined by the claims and elaborated in the specification. An inhaler dosage that proved successful (see the O'Byrne *et al.* article described above) was explicitly taught in the specification; moreover, there is no reason to suppose it is the only dosage that would work. Duration of treatment is as long as needed, as these are asthma patients and presumably will need prevention and treatment indefinitely. There is no reason to think the carrier is critical. The only thing here difficult to envision is why the Examiner believes practicing the claimed invention would require an undue degree of experimentation.

A careful consideration of all of the Wands factors and the evidence of record in this case makes it clear that the Examiner's concerns regarding enablement of the "prevention" aspect of the present claims are unwarranted. Appellant maintains that the claims are enabled and respectfully requests that the Board reverse the rejection under 35 U.S.C. § 112, first paragraph.

II. Rejections under 35 U.S.C. § 103(a)

A. Rejection of claims 13-15, 17, 18, 20-36, 38, 42, and 43 for obviousness over Carling *et al.*

Claims 13-15, 17, 18, 20-36, 38, 42, and 43, stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Carling *et al.* (WO 93/11773, "New Combination of Formoterol and Budesonide").

Analysis and determination of obviousness under § 103(a) requires determination of the scope and content of the prior art, differences between the prior art and the claims in issue, and the level of ordinary skill in the pertinent art. Graham v. John Deere, 383 U.S. 1, 17 (1966). See also MPEP 2141(I). When applying § 103(a), the examiner must consider the claimed invention as a whole; must consider the cited reference as a whole; and must view the reference without the benefit of impermissible hindsight vision afforded by the claimed invention. MPEP 2141(II). Any rejection of a claim for obviousness must establish that the prior art contains a motivation to alter the teachings of the art, in order to arrive at the claimed invention. In re Vaeck, 947 F2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). In addition, the examiner's *prima facie* case must include a finding that one of ordinary skill in the art at the time the invention was made would have reasonably expected the claimed invention to work. *See*, Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd., 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991). Such objective considerations as surprising results (In re Soni, 54 F.3d 746, 34 USPQ2d 1684 (Fed. Cir. 1995)), long felt but unsolved need (Dow Chem. Co. v. American Cyanamid Co., 816 F.2d 617, 622, 2 USPQ2d 1350, 1355 (Fed. Cir. 1987), and skepticism of experts (United States v. Adams, 383 U.S. 39, 148 USPQ 479 (1966)) are also relevant to the obviousness inquiry.

All of the present claims except claim 43 are drawn to methods of prevention and treatment of asthma symptoms, which methods comprise instructing a patient to inhale an effective amount of a combination of active ingredients comprising formoterol (or a pharmaceutically acceptable salt or solvate thereof or a solvate of such a salt) and budesonide. These claims differ in the details of the instructions to the patient, as follows. Independent claim 13 requires that the patient be instructed to inhale the composition **on demand, as determined by the patient** based on the patient's symptoms, as a treatment and a preventive measure, when the patient experiences an increase in asthma symptoms. Independent claim 35

requires that the patient be instructed to inhale the composition **on demand, as determined by the patient** based on the patient's symptoms, as a complement to maintenance treatment of patient's asthma. Independent claim 36 requires that the patient be instructed to inhale the composition **on demand, as determined by the patient,** when the patient is expecting to encounter an asthma triggering event, as a preventative measure. Independent claim 42 requires that the patient be instructed to take a maintenance dose of the composition, and, if the patient experiences asthma symptoms, to inhale additional doses **as needed** to improve control and provide acute relief. And finally, independent claim 43 is drawn to a method of "reducing the incidence of acute asthma attacks" by instructing the patient to inhale an effective amount of the same combination of active ingredients, where the patient is instructed to inhale the composition **on demand, as determined by the patient** based on the patient's symptoms, as a treatment and to reduce the incidence of acute asthma attacks, when the patient experiences an increase in asthma symptoms.

It can be seen from the above that each of the claims is limited to methods in which the patient is instructed to inhale the formoterol/budesonide composition either "**on demand, as determined by the patient**" or "**as needed**". Arriving at these methods required an insight by Appellant: that leaving to the patient's discretion the question of how many doses of a combination budesonide/formoterol composition to take on any give day, according to the patient's determination of need, would greatly improve control over the patient's asthma and reduce the number of asthma attacks suffered by the patient; and that this could be done without incurring in practice a substantial risk of overdose of budesonide, a potent glucocorticosteroid. This insight was nowhere in the prior art, and in fact represented a radical departure from how patients were instructed to take budesonide-containing compositions prior to 1998, the priority date of the present application.

Carling *et al.*, WO 93/11773, is cited as rendering the claimed methods obvious. Carling *et al.* discloses treatment of asthma by inhalation of a combination of formoterol and budesonide from a single inhaler. According to Carling *et al.* at page 4, lines 19-21, "The combination according to present invention permits a twice daily dosing regime as a basic treatment of asthma, particularly nocturnal asthma." (Emphasis added.) Similarly, page 6, lines 22-29, says, "The intended dose regimen is a twice daily administration...." Such a set,

twice-daily regimen has long been, and still is today, a standard asthma treatment protocol for anti-inflammatory glucocorticosteroids such as budesonide. Commonly termed "maintenance therapy," it is intended to reduce over the long term the chronic inflammation that, if uncontrolled, can contribute to spasms of bronchoconstriction—*i.e.*, acute asthma attacks. Typically the asthma patient will also be prescribed an inhaler containing a short-acting bronchodilator for use as needed to stop an imminent or ongoing attack that occurs despite the glucocorticosteroid maintenance therapy regimen. Use of that short-acting bronchodilator is left to the discretion of the patient. In contrast, use of budesonide or other powerful glucocorticosteroids is not—or at least wasn't until the present invention. As will be clear from evidence discussed in detail below, patients who were prescribed a budesonide-containing inhaler were warned not to take any more (or any fewer) doses from their budesonide inhaler than the two fixed doses per day prescribed by the physician for maintenance therapy. This reflects both what was perceived to be the relatively slow-acting nature of glucocorticosteroids, rendering them mostly useless in an acute attack, and the danger of systemic side effects from overdosing on glucocorticosteroids in general. While the physician had the discretion to adjust the size of the two fixed daily doses of glucocorticosteroid according to factors such as the age and weight of the patient or the severity of the patient's illness, such adjustments were solely at the discretion of the physician. The patient would not make that decision, and the number of administrations of budesonide or other glucocorticosteroid would generally remain at twice per day even if the prescribed fixed dosage per administration were changed by the physician. Evidence supporting these assertions, including statements derived from various inhaler product inserts, is discussed below.

The final Office Action cites Carling *et al.* for its teaching that a composition comprising both formoterol and budesonide can be used to treat asthma, noting that, at pages 7-9, Carling *et al.* "exemplify amounts of the two active agents per dose, which calculate up to 8 inhalation per day without going over the maximum daily dosage" (non-standard English in the original). As best as Appellant can decipher it, the "up to 8 inhalation per day" is a reference to some of Carling *et al.*'s examples of inhalers described on pages 7-9 as delivering 12 μg of formoterol and either 100 or 200 μg budesonide, combined with Carling *et al.*'s teaching on page 6, lines 24-26, that a "suitable daily dose" of formoterol is 6 to 100 μg and a "suitable daily

dose" of budesonide is 50 to 4800 μg. Thus, in theory one could inhale eight "puffs" from an inhaler that delivers a combination of 12 μg formoterol and 100 or 200 μg budesonide per puff without exceeding what Carling *et al.* teaches is the upper end of the range of a suitable daily dose of formoterol (100 μg) and the upper end of the range of a suitable daily dose of budesonide (4800 μg). The reference itself actually says nothing about the number of inhalations per administration, rather only that those inhalations should be grouped into just two administrations per day ("the intended dose regimen is a twice daily administration" (page 6, lines 22-23)) and should deliver a total daily dose within the recommended ranges. Each of the two administrations per day intended by Carling *et al.* could, in theory, involve a single "puff", or two or more "puffs"—whatever is needed to achieve the fixed daily dosage prescribed by the physician using whatever inhaler is commercially available. The mere fact that a particular inhaler delivers a dose that is less than half of a prescribed daily dose does not mean that the prescribed daily dose should be spread out into more than two administrations per day, in contravention of Carling *et al.*'s explicit teachings that the intended dose regimen is twice daily. The Examiner's interpretation to the contrary, which is central to her obviousness theory, is therefore without basis in the reference.

The Examiner recognizes that Carling does not teach that the patient should be instructed to inhale the composition on an "on demand" or "as needed" basis, as required by the claims. As acknowledged in the final Office Action at page 7,

> The difference between Carling *et al.* and Applicant's invention is instructing a patient to inhale, on demand, as determined by the patient based on the patient's symptoms...[and] instructing patient to inhale additional doses as needed if he experiences asthma including acute asthmatic episode...(non-standard English in the original)

The Examiner concludes that despite this lack of explicit teaching in the reference, the instruction required by the claims would have been obvious in view of Carling *et al.*'s teachings:

> However, to instruct the patient to inhale, on demand, as determined by the patient's symptoms in acute asthmatic episode is obvious since Carling *et al.* teach that the dosages strongly depends on the severity of disease (mild, moderate, severe asthma) and the suitable daily dosage is up to 8 inhalations. Final Office Action at page 7.

In order to arrive at this conclusion, the Examiner had to make two assumptions about the Carling *et al.* reference: *first*, that Carling *et al.* can be read as teaching that the maximum daily dose of the active ingredients can be spread out in as many as eight discrete administrations over the course of the day, and *second*, that Carling *et al.* suggests that it is up to the patient to determine how many of those eight administrations to take on any given day, based on "severity of disease". The lack of basis for the *first* assumption is discussed above. The *second* assumption is even more far-fetched than the first. It seems to derive from the sentence at page 6, lines 27, of Carling *et al.* that "[the] particular dose used will strongly depend on the patient (age, weight etc) and the severity of the disease (mild, moderate, severe asthma etc)." This sentence of course was intended to mean that the physician will determine a fixed dose that depends on the patient's age, weight, and severity of disease, and not that the physician should instruct the patient to make these determinations for himself or herself. In fact, it seems fairly ridiculous to have to explain that point at all. The twice-daily dose regimen called for by Carling *et al.* is a fixed dosage prescribed by the physician for the patient to inhale two times per day, every day, no more and no less, consistent with what was known in the art about administration of any budesonide-containing composition for treatment or prevention of asthma symptoms. The amount inhaled at each administration can be varied only by a change in the prescription by the physician, again consistent with what was known in the art about administration of any budesonide-containing composition in the asthma context. This is neither "on demand" nor "as needed." It is fixed.

As evidence that one of ordinary skill in the art of asthma therapy would have agreed with Appellant's interpretation of Carling *et al.*, and not with the Examiner's interpretation, Appellant refers the Board to certain exhibits submitted with the Amendment dated June 29, 2005. The exhibits are attached to and referenced in the Evidence Appendix (appendix (ix)) below as Exhibits A-F. The exhibits show that from a date prior to the present priority date to as late as 2003, glucocorticosteroid-containing therapeutics were routinely prescribed for fixed-dosage use twice per day as maintenance therapy, with the patient forbidden to vary daily dosage outside that regimen, whether "on demand," "as needed", or for any other reason. Once one understands how inhaled glucocorticosteroids such as budesonide were typically prescribed for

asthma patients prior to Appellant's invention, it is apparent that Appellant's (and not the Examiner's) interpretation of Carling *et al.* is the one that a person of ordinary skill would have taken from this reference.

Certain sections of these Exhibits have been circled and labeled in the margin with a capital letter for ready reference.

The glucocorticosteroid budesonide is the sole active ingredient in an inhaler sold under the trademark Pulmicort® Turbuhaler® for maintenance treatment of asthma. A copy of a 1997 product insert packaged with the Pulmicort® Turbuhaler® product is submitted as Exhibit A. Recommended starting doses and highest recommended doses for various categories of patients are set out in a table in this document (Exhibit A, page 4, section A); each and every one of these doses is to be administered "twice daily." There is no provision for additional doses to be taken "as needed." Indeed, the section titled "Patient's Instructions for Use" on page 2 of the document (see entire bottom half of page 2) repeatedly and emphatically instructs the patient not to take more or less than the exact dose prescribed by the physician, regardless of whether the patient is feeling better or worse on a given day.

The patient instructions concerning dosage (labeled as section B on page 2 of Exhibit A) are quoted in their entirety below:

DOSAGE

- Use as directed by your doctor.
- It is **VERY IMPORTANT** that you follow your doctor's instructions as to how many inhalations to take and how often to use your Pulmicort Turbuhaler
- **DO NOT** inhale more doses or use your Pulmicort Turbuhaler more often than your doctor advises.
- It may take 1 to 2 weeks or longer before you feel maximum improvement so **IT IS VERY IMPORTANT THAT YOU USE PULMICORT TURBUHALER REGULARLY. DO NOT STOP TREATMENT OR REDUCE YOUR DOSE EVEN IF YOU ARE FEELING BETTER**, unless told to do so by your doctor.
- If you miss a dose, just take your regularly scheduled next dose when it is due. **DO NOT DOUBLE** the dose. (Emphasis in original).

These instructions provide objective evidence that the paradigm for treatment of asthma with budesonide in 1997 was for a physician to prescribe a particular number of doses (generally two) per day for a patient and instruct the patient to take exactly that number of doses, no more or less. The third and last bullet points of the above instructions are particularly telling. Under no circumstances was the patient to take more doses than the specific number prescribed by the physician. Even if the patient missed a dose, the patient was not to take even a single extra dose. This is directly contrary to the Examiner's assertion that

> the skilled artisan would have been motivated to instruct the patient to use Carling *et al.*'s composition as needed bases up to 8 inhalations a day with reasonable expectation of successfully achieving maximum benefit in treatment of any severity condition of asthma in general including acute asthmatic condition. (Final Office Action at page 8; non-standard English in the original.)

Exhibit A also says:

> Patients should take the medication as directed and use PULMICORT TURBUHALER at regular intervals twice daily since its effectiveness depends on regular use. The patient should not alter the prescribed dosage unless advised to do so by the physician....If symptoms do not improve in that time frame, or if the condition worsens, the patient should be instructed to contact the physician. (Exhibit A, page 3, section C.)

This further illustrates that the physician, and not the patient, determines when the dosage of budesonide can be altered for a given patient. If the patient suffers an exacerbation of symptoms,

he must turn to a different type of medication (a short-acting bronchodilator) for immediate relief: **"PULMICORT TURBUHALER is not a bronchodilator and is not indicated for rapid relief of bronchospasm or other acute episodes of asthma."** Exhibit A, page 2, section D.

"PULMICORT TURBUHALER is contraindicated in the primary treatment of status asthmaticus or other acute episodes of asthma where intensive measures are required." Exhibit A, page 1, section E.

"If used at excessive doses for prolonged periods, systemic corticosteroid effects such as hypercorticism may occur." Exhibit A, page 3, section F.

"Since budesonide is absorbed into the circulation and can be systemically active at higher doses, the full beneficial effects of PULMICORT TURBUHALER in minimizing HPA [hypothalamic-pituitary-adrenal] dysfunction [a deleterious side-effect of glucocorticosteroid overdosing] may be expected only when recommended dosages are not exceeded and individual patients are titrated to the lowest effective dose." Exhibit A, page 3, section G.

These warnings make it clear that budesonide was understood to be useful for long-term prevention of asthma symptoms when used regularly in a fixed dose that is set (and carefully monitored) by the physician according to the patient's needs, but had no role in short-term relief of acute symptoms. The only medication that could be taken by the patient on an as-needed basis was a short-acting bronchodilator. The physician was explicitly directed to ensure that the patient received the lowest effective fixed dose of budesonide. Even in 1997 (four years after Carling *et al.*), instructing the asthmatic patient to take additional doses of a budesonide composition on an as-needed basis, *i.e.*, at the patient's own discretion, was strictly forbidden. There was no evidence that taking budesonide more frequently or in larger doses than prescribed would be of any benefit to the patient, and there was a significant risk of harm.

That 1997 product insert pertains to budesonide alone, rather than a combination product. There are now at least two combination glucocorticosteroid/bronchodilator inhalation products (comparable to the combination product disclosed by Carling *et al.*) on the market for treatment of asthma. Product inserts for the two marketed products are presented as Exhibits B and C. As

elaborated below for both products, the physician instructs the patient to inhale a set dose, twice per day--consistent with Appellant's (and not the Examiner's) interpretation of Carling *et al.*

The first combination product is SYMBICORT TURBUHALER, a budesonide/formoterol inhalation powder product similar to that disclosed by Carling *et al.* Exhibit B is a product insert circa 2001 for that product. It says that the "**recommended dosage**" is 1-2 inhalations twice daily (Exhibit B, page 1, section A); when control of symptoms is achieved with the twice daily regimen, the physician can choose to reduce the number of inhalations to one daily (Exhibit B, page 1, section B).

The insert instructs the physician to adjust the dosage to reflect the severity of the particular patient's disease: "**The dosage of the components of Symbicort Turbuhaler is individual and should be adjusted to the severity of the disease. This should be considered when treatment with combination products is initiated.**" Exhibit B, page 1, section C.

There is no suggestion anywhere in the document that the patient can be instructed to take it "as needed." To the contrary, use outside of the fixed dose is dangerous and forbidden: **"If patients find the treatment ineffective, or exceed the current dose of the fixed combination, medical attention must be sought."** Exhibit B, page 2, section D.

Moreover, "**increasing use of rescue bronchodilators indicates a worsening of the underlying condition and warrants a reassessment of the asthma therapy**"; **"patients should be regularly reassessed by a doctor, so that the dosage of Symbicort Turbuhaler remains optimal. The dose should be titrated to the lowest dose at which effective control of symptoms is maintained."** Exhibit B, page 2, section E; and page 1, section F, respectively (emphasis added).

These instructions clearly indicate that if the patient experiences an increase or decrease in symptoms, the patient is to notify the physician so that the treatment protocol can be reassessed (and if necessary, adjusted) by the physician. Adjusting the dosage from day to day at the patient's discretion is nowhere contemplated.

The second combination product is the Advair Diskus® fluticasone propionate/salmeterol xinafoate inhalation powder product. This combination is prescribed for use twice per day, at a dose set by the physician. (Like budesonide, fluticasone propionate is a glucocorticosteroid, and like formoterol, salmeterol xinafoate is a beta-2 agonist.) The Patient's Instructions for Use

(March 2003) for this product, attached as Exhibit C, emphasizes repeatedly that the product must be used neither more nor less often than instructed by the physician. The pertinent portion of these instructions, found on page 2 of the insert, is reproduced below:

2. It is important that you inhale each dose as your doctor has advised. The label will usually tell you what dose to take and how often. If it doesn't, or if you are not sure, ask your doctor or pharmacist. **Do not use ADVAIR DISKUS more frequently than 2 times daily, morning and evening, approximately 12 hours apart, at the recommended dose of 1 inhalation each time.**
3. ADVAIR DISKUS delivers your dose of medicine as a very fine powder **that most, but not all, patients can taste or feel.** Whether or not you are able to taste or feel your dose of medicine, you should not exceed the recommended dose of 1 inhalation each morning and evening, approximately 12 hours apart. If you are not sure you are receiving your dose of ADVAIR DISKUS, contact your doctor or pharmacist.
4. You may feel better after the first dose of ADVAIR DISKUS; however, it may take 1 week or longer to achieve maximum benefit. It is **IMPORTANT THAT YOU USE ADVAIR DISKUS REGULARLY. DO NOT STOP TREATMENT EVEN IF YOU ARE FEELING BETTER** unless told to do so by your doctor.
5. If you miss a dose, just take your next scheduled dose when it is due. **DO NOT DOUBLE** the dose.
6. **DO NOT USE ADVAIR DISKUS TO *RELIEVE* SUDDEN ASTHMA SYMPTOMS** (e.g., sudden severe onset or worsening of wheezing, cough, chest tightness, and/or shortness of breath that has been diagnosed by your doctor as due to asthma). **An inhaled, short-acting bronchodilator such as albuterol should be used to *relieve* sudden asthma symptoms.** If you do not have an inhaled, short-acting bronchodilator, contact your doctor to have one prescribed for you. **You should continue to take ADVAIR DISKUS as instructed by your doctor.**

The patient is adamantly instructed not to use the combination therapy more frequently than 2 times daily, spaced approximately 12 hours apart, and is told to inhale only the recommended dose of 1 inhalation each time. The patient is further instructed not to use the product to relieve sudden asthma symptoms. Like the evidence discussed above, this evidence (from 2003) is directly contrary to the Examiner's assertions regarding what would have been "obvious" to one of ordinary skill in the art ten years earlier, in view of Carling *et al.* in 1993.

Clearly even as late as 2003 (long after the 1998 priority date of the present application), glucocorticosteroid-containing inhaled therapeutics were routinely prescribed solely for fixed-dosage use as maintenance therapy, and not for immediate relief of worsening symptoms. One of ordinary skill in the art of inhaled glucocorticosteroid therapy for treatment of asthma would have understood in 1998 that patients were never instructed to take inhaled glucocorticosteroids

on an "as needed basis." Carling *et al.* would certainly not have been read as recommending such a radical—and potentially dangerous—departure from the norm.

Further evidence concerning the proper interpretation of Carling *et al.* is provided by the publications submitted herewith as Exhibits D and E, both made of record in the Amendment filed June 29, 2005. Exhibit D is a journal article (O'Byrne *et al.*, "Budesonide/Formoterol Combination Therapy as Both Maintenance and Reliever Medication in Asthma," *Am J Respir Crit Care Med* 171:129-136, 2005) discussing the positive results of a recent clinical trial studying the efficacy of Appellant's claimed method for reducing the incidence of asthma exacerbations and other asthma symptoms. This article was discussed above in the part of this brief addressing the rejection for lack of enablement under 35 U.S.C. § 112, paragraph 1. Exhibit E (Barnes, "A Single Inhaler for Asthma?" *Am J Respir Crit Care Med* 171:95-96, 2005) is an editorial, in the same journal issue. Dr. Barnes states his opinion that "the study by O'Byrne and his colleagues may lead to changes in the paradigm of asthma management...." Exhibit E, page 95, last paragraph, emphasis added. Moreover, Dr. Barnes views the success of Appellant's treatment protocol as "remarkable", even several years after Appellant's priority date:

> The remarkable, and somewhat unexpected, finding was that the treatment with combination inhaler for both maintenance and relief markedly reduced the number of severe exacerbations (the primary outcome measure) over the 1-year treatment period compared with other treatments, but also reduced the need for oral corticosteroids, improved symptom control, and lung function compared with the other treatment regimens. (page 95, col.1, last paragraph)

Dr. Barnes explains in the carryover sentence of col.1-2 one reason why this approach was not previously contemplated: "A concern about this approach is that some patients might end up using the combination inhaler frequently and therefore receive an unacceptably high dose of inhaled corticosteroid." He then notes that this turned out not to be a problem in practice. In fact, the patients instructed to take the budesonide/formoterol combination on an as-needed basis inhaled on average only one additional dose per day, yet this approach was more effective in preventing exacerbations than doubling the fixed daily amount of budesonide had proven in a different study. Dr. Barnes notes that these are "surprisingly good results" (page 95, col.2, first full paragraph).

It is to be kept in mind that these statements by Dr. Barnes, including the characterization of the O'Byrne *et al.* report as including "surprisingly good results," were made in 2005, twelve years after the Carling *et al.* reference was published. In the heavily researched field of asthma treatment, if Appellant's invention had indeed been obvious from Carling *et al.*'s teachings, it would not, twelve years later, have been regarded as the radical departure from the norm implied by the Barnes editorial. As the Federal Circuit stated in Environmental Designs, Ltd. v. Union Oil Co. of Cal., 713 F.2d 693, 698 (Fed. Cir. 1998), "Expressions of disbelief by experts constitute strong evidence of nonobviousness." See also MPEP 716.05. Barnes' objective characterization of Appellant's treatment as "remarkable" and the results as "surprisingly good" certainly qualifies as strong evidence of nonobviousness.

The Supreme Court in Graham explained that, to reach a proper determination under 35 U.S.C. § 103, the Examiner must step backward in time and into the shoes worn by the hypothetical "person of ordinary skill in the art" when the Appellant's invention was unknown and just before it was made. "The importance of resolving the level of ordinary skill in the art lies in the necessity of maintaining objectivity in the obviousness inquiry." Ryko Mfg. Co. v. Nu-Star, Inc., 950 F.2d 714, 718 (Fed. Cir. 1991). In view of all factual information, the Examiner must then make a determination whether the claimed invention "as a whole" would have been obvious at that time to that person. MPEP 2141.

The exhibits presented here (particularly Exhibit A) help to establish the level of ordinary skill in the art at the time of Carling *et al.* and at the filing date of Appellant's application. With this level of ordinary skill in the art in mind, Appellant turns to the question of whether the Examiner has met her burden of establishing (1) that the prior art contains a motivation to arrive at the presently claimed methods (In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)); and (2) that one of ordinary skill in the art would have reasonably expected the claimed invention to work (Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd., 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991)), both being essential elements of any *prima facie* case of obviousness. These elements are addressed in turn.

Motivation: The Examiner's position regarding motivation is set forth at pages 7-8 of the final Office Action. Appellant understands the Examiner's position to stem from a combination of certain interpretations of Carling *et al.*, which Appellant restates as follows:

(a) the Examiner's deduction that the maximum dosage recommended by Carling *et al.* at page 6, lines 24-27, can be divided into eight separate inhalations;
(b) the Examiner's conclusion that, because the eight inhalations add up to no more than Carling *et al.*'s maximum suggested daily dose, all eight could be "safely inhaled" by a patient on any given day, at the patient's discretion; and
(c) the Examiner's view that Carling *et al.*'s statement on page 6, lines 27-29, that "[the] particular dose used will strongly depend on the patient (age, weight etc) and the severity of the disease (mild, moderate, severe asthma etc)" means that the patient should be instructed to make the determination of his/her dosage on any given day, up to a total of eight inhalations.

Appellant believes these interpretations of Carling *et al.*'s teachings are not accurate representations of how one of ordinary skill in the art of asthma treatment would have read this reference. For example, the Examiner has made the breathtakingly unwarranted assumption (paraphrased in part (b) above) that every asthma patient will be able to "safely inhale" even the high end of the ranges of "suitable daily doses" set forth at page 6, lines 24-27, of Carling *et al.* (the ranges being 6-100 μg of formoterol and 50-4800 μg of budesonide). Even if Carling *et al.* hadn't gone on to explain that the "particular dose" depends "strongly" on patient-specific factors ("the particular dose used will strongly depend on the patient (age, weight etc) and the severity of the disease (mild, moderate, severe asthma etc)," one of ordinary skill in the art of asthma treatment would clearly not have read Carling *et al.*'s teachings about dosage ranges as meaning <u>all</u> patients can safely inhale <u>all</u> doses up to and including the maximum. That simply is not reasonable. Young children, for example, would not be able to safely inhale the same daily dosage that a 200 lb. adult could handle. Further, the Examiner's assumption is inconsistent with the knowledge in the art that budesonide and other glucocorticosteroids are potent drugs with dangerous side effects, whose use must be carefully monitored in every patient to avoid overdosing (see evidence to that effect discussed above).

Appellant has previously explained why the Examiner's interpretation of Carling *et al.*'s statement quoted in part (c) above is far off base. Carling *et al.*'s reference to "severity of the disease" as being one of the bases for setting the amount of the twice-daily dose of the composition does <u>not</u> mean that the patient should be told to take more doses if his/her disease is particularly severe on a given day. It simply means that the overall level of the patient's disease

is one of the factors (along with the patient's age, weight, etc.) the prescribing physician should take into account in setting the twice-daily dose. Thus, this statement cannot be read as providing any motivation to instruct the patient to inhale the composition "on demand" or "as needed", as required by the present claims. Without a motivation to alter Carling *et al.*'s teachings to arrive at the presently claimed methods, the obviousness rejection fails.

Expectation of Success: The statement in the final Office Action that seems to communicate the Examiner's view regarding "expectation of success" is at page 8:

> The skilled artisan would have been motivated to instruct the patient to use Carling's composition as needed bases up to 8 inhalations a day with reasonable expectation of successfully achieving maximum benefit in treatment of any severity condition of asthma in general including acute asthmatic condition. (Non-standard English in original)

As Appellant understands it, the Examiner is saying that one of ordinary skill would have a reasonable expectation of successfully treating any and all asthma patients by simply handing them an inhaler containing Carling *et al.*'s formoterol /budesonide composition and telling them to inhale any amount per day that they wish, up to and including the maximum daily dose of 100 μg formoterol and 4800 μg budesonide, because that will give them "maximum benefit." Appellant points out that Carling et al. warns the reader that the particular dose of the combination "will strongly depend" on patient-specific factors, factors that are not normally left to the judgment of the patient. While Carling et al. was referring to a fixed, twice-daily dose (there being no allowance in Carling et al. for anything other than a fixed, twice-daily dose), the same would certainly be true of any additional doses taken each day. Further, at least with respect to the budesonide part of this composition, Appellant has provided ample evidence that one of ordinary skill in 1997 would NOT have had such a reasonable expectation of success under the scenario the Examiner believes is "obvious". In fact, the very idea would have shocked the medical establishment. (See above discussion of Exhibit A.) This view apparently had not changed by 2001 when the formoterol/budesonide combination product was marketed with a product insert warning the user not to exceed the fixed, twice-daily dosage prescribed by the physician. (See above discussion of Exhibit B.) Because the Examiner has not established that one of ordinary skill at the 1998 priority date would have had a reasonable expectation that the claimed methods would succeed, her *prima facie* case of obviousness must fail.

The above evidence and arguments demonstrate that the Examiner has not met her burden in making out a *prima facie* case of obviousness. Accordingly, it is unnecessary for Appellant to come forward with objective evidence to rebut the Examiner's case. However, such evidence is already of record, so Appellant will bring it to the Board's attention as a further (and powerful) indication of the non-obviousness of the presently claimed methods. Graham. Such objective evidence must be taken into account by the Examiner. In re Soni.

First, Appellant points to the objective evidence of ***surprising results*** embodied in Exhibit D, the O'Byrne *et al.* journal article discussed above. The authors conducted clinical trials to compare three different treatment regimens for asthma. The relevant features of the Study Design (page 130, first column) are summarized here:

In the first treatment arm (nicknamed "bud/form maintenance + relief") of the O'Byrne *et al.* study, the patients were instructed to use a budesonide/formoterol combination inhaler twice per day, every day, for maintenance, plus the same inhaler for relief of symptoms on an as-needed basis, as determined by the patient. This first treatment arm was thus instructed in accordance with the present claims.

Patients in the second treatment arm ("bud/form + SABA") were instructed to use the same budesonide/formoterol combination inhaler just twice per day, and no more: *i.e.*, for maintenance therapy only. A second inhaler containing a different drug, the short-acting bronchodilator terbutaline, was provided to the patients of this second treatment arm for use as needed for immediate relief of acute asthma symptoms. Since this second treatment arm received the budesonide/formoterol combination just twice per day, as explicitly taught by Carling *et al.*, it is representative of the closest prior art identified by the Examiner.

Patients in the third treatment arm ("bud + SABA") were instructed to use a budesonide-only inhaler just twice per day. For relief of acute symptoms, these patients used a second inhaler containing terbutaline as needed. This third treatment arm thus represents the prior art such as in the Pulmicort Turbuhaler® 1997 product insert of Exhibit A, in which a budesonide-only inhaler was used for maintenance therapy twice per day, and the patient was instructed to use a separate bronchodilator product as needed for relief of acute symptoms (see the section labeled "I" on page 2 of Exhibit A).

As shown in the first bar graph of Figure 1B of O'Byrne *et al.*, instructing the patient in accordance with the present claims dramatically decreased the total number of severe exacerbations (acute asthma attacks) experienced by those patients, compared to the total number experienced by patients instructed to follow either of the prior art methods. Table 2 analyzes the data in another way: only 16% of the patients instructed in accordance with the present claims experienced severe exacerbations, compared to 27% or 28% of the patients in the two prior art treatment arms, respectively. Similarly striking differences were seen in many other measures described in detail in the Results section on page 130, in Figures 1 and 2, and in Table 2. Rather than lengthen this already-long brief any further, Appellant urges the Board to study the article if additional evidence of surprising results is deemed needed. In view of this article, it is irrefutable that the presently claimed method produces results that are unexpectedly better than what the prior art methods produce.

Second, Appellant notes that two additional Graham-derived categories of objective indicia of nonobviousness are embodied in the editorial by Peter J. Barnes, M.D., attached as Exhibit E: ***long felt, unsatisfied need*** and ***skepticism of experts***, as well as support for the ***surprising results*** nature of the O'Byrne *et al.* results. Dr. Barnes is an expert in the field of asthma therapies who is associated with the National Heart and Lung Institute, Imperial College, London, UK. His editorial, which is also discussed above in another context, opines regarding the significance of the O'Byrne *et al.* clinical results.

Dr. Barnes begins with the following statement of long felt, unsatisfied need for an effective asthma treatment: "Despite the availability of highly effective therapies, many patients with asthma continue to suffer symptoms and exacerbations, with considerable disruption to their daily life." Barnes goes on to discuss O'Byrne *et al.*'s findings that treatment with combination inhaler for both maintenance and relief "markedly reduced the number of severe exacerbations...over the 1-year treatment period compared with the other treatments", and also "reduced the need for oral corticosteroids, improved symptom control, and lung function compared with the other treatment regimens," implying that here at last may be a way to satisfy that long felt need, at least for many patients inadequately served by prior therapies. Dr. Barnes offers his view that the O'Byrne et al. study "may lead to changes in the paradigm of asthma management," another indication that he believe it is at least a partial answer to the long felt

need. Dr. Barnes also describes what amounts to past skepticism of experts regarding the claimed method: "A concern about this approach is that some patients might end up using the combination inhaler frequently and therefore receive an unacceptably high dose of inhaled corticosteroid." He then reassures the reader: "However, this was not the case, as the mean number of additional doses of combination inhaler was only one dose per day and very few patients used high doses." Finally, the editorial makes the point that the O'Byrne et al. findings were "remarkable" and "surprisingly good results," supporting quite literally Appellant's thesis that the present claimed methods produce surprising results compared to both the prior art Carling *et al.* method and the prior art budesonide-only method, results that could not have been predicted in view of any of this prior art.

It is clear from the Exhibits and the arguments presented above that one of ordinary skill in the art of asthma therapy at the priority date would not have interpreted Carling *et al.* as suggesting that patients should be instructed to inhale a budesonide-containing product "on demand" or "as needed". The paradigm for use of budesonide-containing products dictated fixed dosage use for maintenance therapy, not variable dosage as determined day-to-day by the patient for relief of an acute attack. And certainly Carling *et al.* gave no reason to expect the surprisingly good results reported by O'Byrne *et al.*

Because Carling *et al.* does not teach or suggest administration of a combination of budesonide and formoterol on demand or as needed as required by the claims, and the level of one of ordinary skill in asthma therapy at the filing date of Appellant's application would not have read Carling *et al.* to describe such methods, the independent claims are not obvious in view of Carling *et al.*

Claims 14, 15, 17, 18, 20-34, and 38 depend from claim 13; they are therefore patentable over Carling *et al.* for at least the reasons discussed above.

In view of the foregoing, the rejection of claims 13-15, 17, 18, 20-36, 38, 42, and 43 as obvious in view of Carling *et al.* is unwarranted, and should be reversed.

B. Rejection of Claims 16 and 19 for obviousness over Carling *et al.* and further in view of Aberg *et al.* and Ryrfeldt *et al.*

Claims 16 and 19 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentably obvious over Carling *et al.* (as applied to claims 13-15, 17, 18, 20-36, 38, 42, and 43) and further in view of Aberg *et al.* (U.S. Patent 5,795,564) and Ryrfeldt *et al.* ("Pulmonary disposition of the potent glucocorticoid budesonide, evaluated in an isolated perfused rat lung model," *Biochem. Pharmacol.* 38:17-22, 1989, Abstract). The Examiner stated at page 9 of the final Office Action that "Carling *et al.* do teach the isomer of formoterol set forth in claim 16 and the specified epimer of budesonide set forth in claim 19." Appellant finds no such teaching in Carling *et al.* Since the Examiner did not respond to Appellant's request (in the Response dated November 15, 2005) to point out where in Carling *et al.* the Examiner found those teachings, Appellant assumes that this statement was simply made in error. Perhaps the Examiner meant to say the inverse: *i.e.*, "Carling *et al.* do not teach..."

The final Office Action also stated at page 9 that

> it would have been obvious to one of ordinary skill in the art to employ (R,R) enantiomer of formoterol and 22R epimer of budesonide in view of Aberg *et al.* and Ryrfeldt *et al.* because both of the references of Aberg and Ryrfeldt teach specific isomers form that possesses potent asthmatic effect of the active agents utilized in Carling reduced adverse effects in treatment of asthma. One would have been motivated to employ (R,R) isomer of formoterol and 22R epimer of budesonide in Carling's composition with reasonable expectation of successfully treating asthmatic patients with reduced adverse effects. (non-standard English in the original)

Claims 16 and 19, which depend from claim 13, are patentable for at least the reasons discussed above with respect to claim 13 and the rest of the independent claims. The teachings of Aberg *et al.* and Ryrfeldt *et al.* do not make up for Carling *et al.*'s deficiencies as outlined above, and indeed are cited solely for their teachings concerning specific epimers of the active ingredients. Accordingly, Appellant requests that the rejection of claims 16 and 19 under § 103(a) be reversed.

CONCLUSION

For the reasons set forth above, Appellant respectfully requests that the rejections of claims 13-36, 38, 42, and 43 be withdrawn.

An attached Claims Appendix (viii) contains a copy of the claims under appeal.

An Evidence Appendix (ix) refers to attached Exhibits A-F.

A Related Proceedings Appendix (x) is attached as required, but contains no subject matter.

The appeal brief fee of $500 required by 37 C.F.R. § 41.20(b)(2) is enclosed. Please apply any other necessary charges, or any credits, to Deposit Account No. 06-1050, referencing Attorney Docket No. 06275-188001.

Respectfully submitted,

Date: March 3, 2002

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(viii) Claims Appendix

13. A method of prevention and treatment of asthma symptoms, which comprises instructing a patient to inhale an effective amount of a composition comprising, in admixture:

(a) a first active ingredient which is formoterol, a pharmaceutically acceptable salt or solvate thereof or a solvate of such a salt; and

(b) a second active ingredient which is budesonide;

characterized in that the patient is instructed to inhale the composition on demand, as determined by the patient based on the patient's symptoms, as a treatment and a preventive measure, when the patient experiences an increase in asthma symptoms.

14. The method according to claim 13, wherein the molar ratio of (a) to (b), calculated as formoterol to budesonide, is from 1:1 to 1:100.

15. The method according to claim 13, wherein the first active ingredient is formoterol fumarate dihydrate.

16. The method according to claim 13, wherein the first active ingredient is the R,R enantiomer of formoterol, a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt.

17. The method according to claim 15, wherein the composition is in the form of unit doses, each of which delivers 1 μg to 48 μg of the first active ingredient to the patient, calculated as formoterol fumarate dihydrate.

18. The method according to claim 15, wherein the patient is instructed to inhale an amount per day of the composition, including for maintenance therapy, that contains a total of 1 μg to 100 μg of the first ingredient, calculated as formoterol fumarate dihydrate.

19. The method according to claim 13, wherein the second active ingredient is the 22R epimer of budesonide.

20. The method according to claim 13, wherein the composition is in the form of unit doses, each of which delivers 20 μg to 1600 μg of budesonide to the patient.

21. The method according to claim 13, wherein the patient is instructed to inhale an amount per day of the composition, including for maintenance therapy, that contains a total of 20 μg to 4800 μg of budesonide.

22. The method according to claim 13, wherein the particle size of the active ingredients (a) and (b) is less than 10 μm.

23. The method according to claim 13, wherein the composition additionally comprises one or more pharmaceutically acceptable additives, diluents or carriers.

24. The method according to claim 13, wherein the composition additionally comprises lactose monohydrate.

25. The method according to claim 14, wherein the molar ratio of (a) to (b), calculated as formoterol to budesonide, is from 1:1 to 1:70.

26. The method according to claim 17, wherein the composition is in the form of unit doses, each of which delivers 3 μg to 12 μg of the first ingredient to the patient, calculated as formoterol fumarate dihydrate.

27. The method according to claim 18, wherein the patient is instructed to inhale an amount per day of the composition, including for maintenance therapy, that contains a total of 2 μg to 60 μg of the first ingredient, calculated as formoterol fumarate dihydrate.

28. The method according to claim 20, wherein the composition is in the form of unit doses, each of which delivers 50 μg to 400 μg of budesonide to the patient.

29. The method according to claim 21, wherein the patient is instructed to inhale an amount per day of the composition, including for maintenance therapy, that contains a total of 30 μg to 3200 μg of budesonide.

30. The method according to claim 13 further comprising instructing the patient to inhale the composition as a rescue medication.

31. The method according to claim 13 further comprising instructing the patient to take a second composition, comprising a glucocorticosteroid, on a regular basis as a maintenance treatment.

32. The method according to claim 13 further comprising instructing the patient to use the composition as a complement to maintenance treatment of the patient's asthma.

33. The method according to claim 13 further comprising instructing the patient to inhale an effective amount of the composition as a preventive measure prior to encountering an asthma triggering event.

34. The method of claim 33 wherein the asthma triggering event is selected from the group consisting of exposure to cold air, exercise, and exposure to a smoky environment.

35. A method of prevention and treatment of asthma symptoms, which comprises instructing a patient to inhale an effective amount of a composition comprising, in admixture:

(a) a first active ingredient which is formoterol, a pharmaceutically acceptable salt or solvate thereof or a solvate of such a salt; and

(b) a second active ingredient which is budesonide;

characterized in that the patient is instructed to inhale the composition on demand, as determined by the patient based on the patient's symptoms, as a complement to maintenance treatment of the patient's asthma.

36. A method of prevention and treatment of asthma symptoms, which comprises instructing a patient to inhale an effective amount of a composition comprising, in admixture:

(a) a first active ingredient which is formoterol, a pharmaceutically acceptable salt or solvate thereof or a solvate of such a salt; and

(b) a second active ingredient which is budesonide;

characterized in that the patient is instructed to inhale the composition on demand, as determined by the patient, when the patient is expecting to encounter an asthma triggering event, as a preventative measure.

38. The method of claim 13 further comprising instructing the patient to use the composition as a complement to maintenance treatment of the patient's asthma.

42. A method of prevention and treatment of asthma symptoms, which comprises instructing a patient to inhale an effective amount of a composition comprising, in admixture:

(a) a first active ingredient which is formoterol, a pharmaceutically acceptable salt or solvate thereof or a solvate of such a salt; and

(b) a second active ingredient which is budesonide;

characterized in that the patient is instructed to take a maintenance dose of the composition, and, if the patient experiences asthma symptoms, to inhale additional doses as needed to improve control and provide acute relief.

43. A method of reducing the incidence of acute asthma attacks, which comprises instructing a patient to inhale an effective amount of a composition comprising, in admixture:

(a) a first active ingredient which is formoterol, a pharmaceutically acceptable salt or solvate thereof or a solvate of such a salt; and

(b) a second active ingredient which is budesonide;

characterized in that the patient is instructed to inhale the composition on demand, as determined by the patient based on the patient's symptoms, as a treatment and to reduce the incidence of acute asthma attacks, when the patient experiences an increase in asthma symptoms.

(ix) Evidence Appendix

Attached are exhibits A-E filed with Appellant's response dated June 29, 2005. The exhibits were acknowledged and entered by the Examiner at pages 10-11 of the final Office Action dated September 21, 2005.

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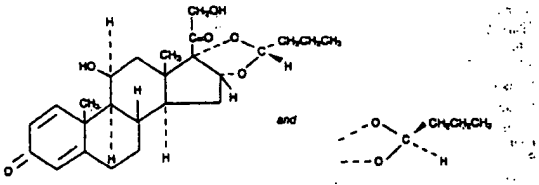
Pulmicort Turbuhaler® 200 mcg

(budesonide inhalation powder)

For Oral Inhalation Only.

DESCRIPTION

Budesonide, the active component of PULMICORT TURBUHALER 200 mcg, is a corticosteroid designated chemically as (RS)-11β,16α,17,21-Tetrahydroxypregna-1,4-diene-3,20-dione cyclic 16,17-acetal with butyraldehyde. Budesonide is provided as a mixture of two epimers (22R and 22S). The empirical formula of budesonide is $C_{25}H_{34}O_6$ and its molecular weight is 430.5. Its structural formula is:



Budesonide is a white to off-white, tasteless, odorless powder that is practically insoluble in water and in heptane, sparingly soluble in ethanol, and freely soluble in chloroform. Its partition coefficient between octanol and water at pH 7.4 is 1.6×10^3.

PULMICORT TURBUHALER is an inhalation-driven multi-dose dry powder inhaler which contains only micronized budesonide. Each actuation of PULMICORT TURBUHALER provides 200 mcg budesonide per metered dose, which delivers approximately 160 mcg budesonide from the mouthpiece (based on *in vitro* testing at 60 L/min for 2 sec). The amount of drug delivered to the lung will depend on patient factors such as inspiratory flow (see Patient's Instructions for Use). In adult patients with asthma (mean FEV_1 2.9 L [0.8 - 5.1 L]) mean peak inspiratory flow (PIF) through PULMICORT TURBUHALER was 78 (40-111) L/min. Similar results (mean PIF 82 [43-125] L/min) were obtained in asthmatic children (6 to 15 years, mean FEV_1 2.1 L [0.9 - 5.4 L]).

CLINICAL PHARMACOLOGY

Budesonide is an anti-inflammatory corticosteroid that exhibits potent glucocorticoid activity and weak mineralocorticoid activity. In standard *in vitro* and animal models, budesonide has approximately a 200-fold higher affinity for the glucocorticoid receptor and a 1000-fold higher topical anti-inflammatory potency than cortisol (rat croton oil ear edema assay). As a measure of systemic activity, budesonide is 40 times more potent than cortisol when administered subcutaneously and 25 times more potent when administered orally in the rat thymus involution assay.

The precise mechanism of corticosteroid actions on inflammation in asthma is not known. Corticosteroids have been shown to have a wide range of inhibitory activities against multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, and lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes, and cytokines) involved in allergic and non-allergic-mediated inflammation. These anti-inflammatory actions of corticosteroids may contribute to their efficacy in asthma.

Studies in asthmatic patients have shown a favorable ratio between topical anti-inflammatory activity and systemic corticosteroid effects over a wide range of doses from PULMICORT TURBUHALER. This is explained by a combination of a relatively high local anti-inflammatory effect, extensive first pass hepatic degradation of orally absorbed drug (85-95%), and the low potency of formed metabolites (see below).

Pharmacokinetics

The activity of PULMICORT TURBUHALER is due to the parent drug, budesonide. In glucocorticoid receptor affinity studies, the 22R form was two times as active as the 22S epimer. *In vitro* studies indicated that the two forms of budesonide do not interconvert. The 22R form was preferentially cleared by the liver with systemic clearance of 1.4 L/min vs. 1.0 L/min for the 22S form. The terminal half-life, 2 to 3 hours, was the same for both epimers and was independent of dose. In asthmatic patients, budesonide showed a linear increase in AUC and C_{max} with increasing dose after both a single dose and repeated dosing from PULMICORT TURBUHALER.

Absorption: After oral administration of budesonide, peak plasma concentration was achieved in about 1 to 2 hours and the absolute systemic availability was 6-13%. In contrast, most of budesonide delivered to the lungs is systemically absorbed. In healthy subjects, 34% of the metered dose was deposited in the lungs (as assessed by plasma concentration method) with an absolute systemic availability of 39% of the metered dose. Pharmacokinetics of budesonide do not differ significantly in healthy volunteers and asthmatic patients. Peak plasma concentrations of budesonide occurred within 30 minutes of inhalation from PULMICORT TURBUHALER.

Distribution: The volume of distribution of budesonide was approximately 3 L/kg. It was 85-90% bound to plasma proteins. Protein binding was constant over the concentration range (1-100 nmol/L) achieved with, and exceeding, recommended doses of PULMICORT TURBUHALER. Budesonide showed little or no binding to corticosteroid binding globulin. Budesonide rapidly equilibrated with red blood cells in a concentration independent manner with a blood/plasma ratio of about 0.8.

Metabolism: *In vitro* studies with human liver homogenates have shown that budesonide is rapidly and extensively metabolized. Two major metabolites formed via cytochrome P450 3A catalyzed biotransformation have been isolated and identified as 16α-hydroxyprednisolone and 6β-hydroxybudesonide. The corticosteroid activity of each of these two metabolites is less than 1% of that of the parent compound. No qualitative difference between the *in vitro* and *in vivo* metabolic patterns have been detected. Negligible metabolic inactivation was observed in human lung and serum preparations.

Excretion: Budesonide was excreted in urine and feces in the form of metabolites. Approximately 60% of an intravenous radiolabelled dose was recovered in the urine. No unchanged budesonide was detected in the urine.

Special Populations: No pharmacokinetic differences have been identified due to race, gender or advanced age.

Pediatric: Following intravenous dosing in pediatric patients age 10-14 years, plasma half-life was shorter than in adults (1.5 hrs vs 2.0 hrs in adults). In the same population following inhalation of budesonide via a pressurized metered-dose inhaler, absolute systemic availability was similar to that in adults.

Hepatic Insufficiency: Reduced liver function may affect the elimination of corticosteroids. The pharmacokinetics of budesonide were affected by compromised liver function as evidenced by a doubled systemic availability after oral ingestion. The intravenous pharmacokinetics of budesonide were, however, similar in cirrhotic patients and in healthy subjects.

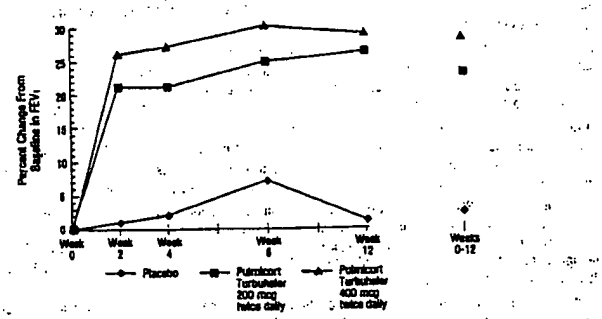
Drug-drug Interactions: Ketoconazole, a potent inhibitor of cytochrome P450 3A, the main metabolic enzyme for corticosteroids, increased plasma levels of orally ingested budesonide. At recommended doses, cimetidine had a slight but clinically insignificant effect on the pharmacokinetics of oral budesonide.

Pharmacodynamics

To confirm that systemic absorption is not a significant factor in the clinical efficacy of inhaled budesonide, a clinical study in patients with asthma was performed comparing 400 mcg budesonide administered via a pressurized metered dose inhaler with a tube spacer to 1400 mcg of oral budesonide and placebo. The study demonstrated the efficacy of inhaled budesonide but not orally ingested budesonide despite comparable systemic levels. Thus, the therapeutic effect of conventional doses of orally inhaled budesonide are largely explained by its direct action on the respiratory tract.

Generally, PULMICORT TURBUHALER has a relatively rapid onset of action for an inhaled corticosteroid. Improvement in asthma control following inhalation of PULMICORT TURBUHALER can occur within 24 hours of beginning treatment although maximum benefit may not be achieved for 1 to 2 weeks, or longer.

A 12-Week Trial in Patients Not on Corticosteroid Therapy Prior to Study Entry

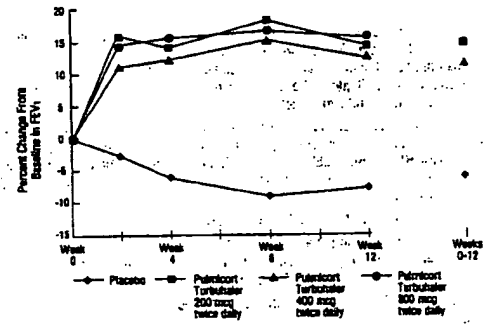


In a 12-month controlled trial in 75 patients not previously receiving corticosteroids, PULMICORT TURBUHALER at 200 mcg twice daily resulted in improved lung function (measured by PEF) and reduced bronchial hyperreactivity compared to placebo.

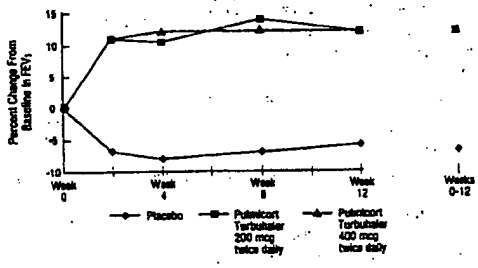
Patients Previously Maintained on Inhaled Corticosteroids

The safety and efficacy of PULMICORT TURBUHALER was also evaluated in adult and pediatric patients (age 6 to 18 years) previously maintained on inhaled corticosteroids (adults: N=473, mean baseline FEV_1 2.04 L, baseline doses of beclomethasone dipropionate 126-1008 mcg/day; pediatrics: N=404, mean baseline FEV_1 2.09 L, baseline doses of beclomethasone dipropionate 126-672 mcg/day or triamcinolone acetonide 300-1800 mcg/day). The FEV_1 results of these two trials, both 12 weeks in duration, are presented in the following figures. Pulmonary function improved significantly with all doses of PULMICORT TURBUHALER compared to placebo in both trials.

Adult Patients Previously Maintained on Inhaled Corticosteroids



Pediatric Patients Age 6 to 18 Years Previously Maintained on Inhaled Corticosteroids



Patients Previously Maintained on Oral Corticosteroids

In a clinical trial in 159 severe asthmatic patients requiring chronic oral prednisone therapy (mean baseline prednisone dose 19.3 mg/day) PULMICORT TURBUHALER at doses of 400 mcg twice daily and 800 mcg twice daily was compared to placebo over a 20-week period. Approximately two-thirds (68% on 400 mcg twice daily and 64% on 800 mcg twice daily) of PULMICORT TURBUHALER-treated patients were able to achieve sustained (at least 2 weeks) oral corticosteroid cessation (compared with 8% of placebo-treated patients) and improved asthma control. The average oral corticosteroid dose was reduced by 83% on 400 mcg twice daily and 79% on 800 mcg twice daily for PULMICORT TURBUHALER-treated patients vs. 27% for placebo. Additionally, 58 out of 64 patients (91%) who completely eliminated oral corticosteroids during the double-blind phase of the trial remained off oral corticosteroids for an additional 12 months while receiving PULMICORT TURBUHALER.

INDICATIONS AND USAGE

PULMICORT TURBUHALER is indicated for the maintenance treatment of asthma as prophylactic therapy in adult and pediatric patients six years of age or older. It is also indicated for patients requiring oral corticosteroid therapy for asthma. Many of those patients may be able to reduce or eliminate their requirement for oral corticosteroids over time.

PULMICORT TURBUHALER is NOT indicated for the relief of acute bronchospasm.

CONTRAINDICATIONS

PULMICORT TURBUHALER is contraindicated in the primary treatment of status asthmaticus or other acute episodes of asthma where intensive measures are required.

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PULMICORT TURBUHALER has been shown to decrease airway reactivity to various challenge models, including histamine, methacholine, sodium metabisulfite, and adenosine monophosphate in hyperreactive patients. The clinical relevance of these models is not certain.

Pretreatment with PULMICORT TURBUHALER 1600 mcg daily (800 mcg twice daily) for 2 weeks reduced the acute (early-phase reaction) and delayed (late-phase reaction) decrease in FEV_1 following inhaled allergen challenge.

The effects of PULMICORT TURBUHALER on the hypothalamic-pituitary-adrenal (HPA) axis were studied in 905 adults and 404 pediatric patients with asthma. For most patients, the ability to increase cortisol production in response to stress, as assessed by cosyntropin (ACTH) stimulation test, remained intact with PULMICORT TURBUHALER treatment at recommended doses. For adult patients treated with 100, 200, 400, or 800 mcg twice daily for 12 weeks, 4%, 2%, 6%, and 13% respectively, had an abnormal stimulated cortisol response (peak cortisol <14.5 mcg/dL assessed by liquid chromatography following short-cosyntropin test) as compared to 6% of patients treated with placebo. Similar results were obtained in pediatric patients. In another study in adults, doses of 400, 800 and 1600 mcg budesonide twice daily via PULMICORT TURBUHALER for 6 weeks were examined; 1600 mcg twice daily (twice the maximum recommended dose) resulted in a 27% reduction in stimulated cortisol (6-hour ACTH infusion) while 10 mg prednisone resulted in a 35% reduction. In this study, no patient on PULMICORT TURBUHALER at doses of 400 and 800 mcg twice daily met the criterion for an abnormal stimulated cortisol response (peak cortisol <14.5 mcg/dL assessed by liquid chromatography) following ACTH infusion. An open-label, long-term follow-up of 1133 patients for up to 52 weeks confirmed the minimal effect on the HPA axis (both basal and stimulated plasma cortisol) of PULMICORT TURBUHALER when administered at recommended doses. In patients who had previously been oral steroid-dependent, use of PULMICORT TURBUHALER in recommended doses was associated with higher stimulated cortisol response compared to baseline following 1 year of therapy.

The administration of budesonide via PULMICORT TURBUHALER in doses up to 800 mcg/day (mean daily dose 445 mcg/day) or via a pressurized metered-dose inhaler in doses up to 1200 mcg/day (mean daily dose 620 mcg/day) to 216 pediatric patients (age 3 to 11 years) for 2 to 6 years had no significant effect on statural growth compared with non-corticosteroid therapy in 62 matched control patients. However, the long-term effect of PULMICORT TURBUHALER on growth is not fully known.

CLINICAL TRIALS

The therapeutic efficacy of PULMICORT TURBUHALER has been evaluated in controlled clinical trials involving more than 1300 patients (6 years and older) with asthma of varying disease duration (<1 year to >20 years) and severity.

Double-blind, parallel, placebo-controlled clinical trials of 12 weeks duration and longer have shown that, compared with placebo, PULMICORT TURBUHALER significantly improved lung function (measured by PEF and FEV_1), significantly decreased morning and evening symptoms of asthma, and significantly reduced the need for as needed inhaled β_2-agonist use at doses of 400 mcg to 1600 mcg per day (200 mcg to 800 mcg twice daily) in adults and 400 mcg to 800 mcg per day (200 mcg to 400 mcg twice daily) in pediatric patients 6 years of age and older.

Improved lung function (morning PEF) was observed within 24 hours of initiating treatment in both adult and pediatric patients 6 years of age and older, although maximum benefit was not achieved for 1 to 2 weeks, or longer, after starting treatment. Improved lung function was maintained throughout the 12 weeks of the double-blind portion of the trials.

Patients Not Receiving Corticosteroid Therapy

In a 12-week clinical trial in 273 patients with mild to moderate asthma (mean baseline FEV_1 2.27 L) who were not well controlled by bronchodilators alone, PULMICORT TURBUHALER was evaluated at doses of 200 mcg twice daily and 400 mcg twice daily versus placebo. The FEV_1 results from this trial are shown in the figure below. Pulmonary function improved significantly on both doses of PULMICORT TURBUHALER compared with placebo.

Hypersensitivity to budesonide contraindicates the use of PULMICORT TURBUHALER.

WARNINGS

Particular care is needed for patients who are transferred from systemically active corticosteroids to PULMICORT TURBUHALER because deaths due to adrenal insufficiency have occurred in asthmatic patients during and after transfer from systemic corticosteroids to less systemically available inhaled corticosteroids. After withdrawal from systemic corticosteroids, a number of months are required for recovery of HPA function.

Patients who have been previously maintained on 20 mg or more per day of prednisone (or its equivalent) may be most susceptible, particularly when their systemic corticosteroids have been almost completely withdrawn. During this period of HPA suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery, or infection (particularly gastroenteritis) or other conditions associated with severe electrolyte loss. Although PULMICORT TURBUHALER may provide control of asthma symptoms during these episodes, in recommended doses it supplies less than normal physiological amounts of glucocorticoid systemically and does NOT provide the mineralocorticoid activity that is necessary for coping with these emergencies.

During periods of stress or a severe asthma attack, patients who have been withdrawn from systemic corticosteroids should be instructed to resume oral corticosteroids (in large doses) immediately and to contact their physicians for further instruction. These patients should also be instructed to carry a medical identification card indicating that they may need supplementary systemic corticosteroids during periods of stress or a severe asthma attack.

Transfer of patients from systemic corticosteroid therapy to PULMICORT TURBUHALER may unmask allergic conditions previously suppressed by the systemic corticosteroid therapy, e.g., rhinitis, conjunctivitis, and eczema (see Dosage and Administration).

Patients who are on drugs which suppress the immune system are more susceptible to infection than healthy individuals. Chicken pox and measles, for example, can have a more serious or even fatal course in susceptible pediatric patients or adults on immunosuppressant doses of corticosteroids. In pediatric or adult patients who have not had these diseases, particular care should be taken to avoid exposure. How the dose, route and duration of corticosteroid administration affects the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed, therapy with varicella zoster immune globulin (VZIG) or pooled intravenous immunoglobulin (IVIG), as appropriate, may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (See the respective package insert for complete VZIG and IG prescribing information.) If chicken pox develops, treatment with antiviral agents may be considered.

PULMICORT TURBUHALER is not a bronchodilator and is not indicated for rapid relief of bronchospasm or other acute episodes of asthma.

As with other inhaled asthma medications, bronchospasm, with an immediate increase in wheezing, may occur after dosing. If bronchospasm occurs following dosing with PULMICORT TURBUHALER, it should be treated immediately with a fast-acting inhaled bronchodilator. Treatment with PULMICORT TURBUHALER should be discontinued and alternate therapy instituted.

Patients should be instructed to contact their physician immediately when episodes of asthma not responsive to their usual doses of bronchodilators occur during treatment with PULMICORT TURBUHALER. During such episodes, patients may require therapy with oral corticosteroids.

PRECAUTIONS

General: During withdrawal from oral corticosteroids, some patients may experience symptoms of systemically active corticosteroid withdrawal, e.g., joint and/or muscular pain, lassitude, and depression, despite maintenance or even improvement of respiratory function.

Patient's Instructions for Use

Pulmicort 200 mcg Turbuhaler
(budesonide inhalation powder)

Pulmicort Turbuhaler® 200 mcg
(budesonide inhalation powder)

Please read this leaflet carefully before you start to take your medicine. It provides a summary of information on your medicine.

FOR FURTHER INFORMATION ASK YOUR DOCTOR OR PHARMACIST.

WHAT YOU SHOULD KNOW ABOUT PULMICORT TURBUHALER

Your doctor has prescribed Pulmicort Turbuhaler 200 mcg. It contains a medication called budesonide, which is a synthetic corticosteroid. Corticosteroids are natural substances found in the body that help fight inflammation. They are used to treat asthma because they reduce the swelling and irritation in the walls of the small air passages in the lungs and ease breathing problems. When inhaled regularly, corticosteroids also help to prevent attacks of asthma.

Pulmicort Turbuhaler treats the inflammation—the "quiet part" of asthma that you cannot hear, see, or feel. When inflammation is left untreated, your asthma symptoms and attacks can increase. Pulmicort Turbuhaler works to prevent and reduce your asthma symptoms and attacks.

IMPORTANT POINTS TO REMEMBER ABOUT PULMICORT TURBUHALER

1. **MAKE SURE** that this medicine is suitable for you (see "BEFORE USING YOUR PULMICORT TURBUHALER" below).
2. It is important that you inhale each dose as your doctor has advised.
3. Use your Turbuhaler as directed by your doctor. **DO NOT STOP TREATMENT OR REDUCE YOUR DOSE EVEN IF YOU FEEL BETTER,** unless told to do so by your doctor.
4. **DO NOT** inhale more doses or use your Turbuhaler more often than instructed by your doctor.
5. This medicine is **NOT** intended to provide rapid relief of your breathing difficulties during an asthma attack. It must be taken at regular intervals as recommended by your doctor, and not as an emergency measure.
6. Your doctor may prescribe additional medication (such as bronchodilators) for emergency relief if an acute asthma attack occurs. Please contact your doctor if:
   - ➢ an asthma attack does not respond to the additional medication,
   - ➢ you require more of the additional medication than usual.
7. If you also use another medicine by inhalation, you should consult your doctor for instructions on when to use it in relation to using your Pulmicort Turbuhaler.

BEFORE USING YOUR PULMICORT TURBUHALER

TELL YOUR DOCTOR BEFORE STARTING TO TAKE THIS MEDICINE:

- ➢ if you are pregnant (or intending to become pregnant),
- ➢ if you are breast-feeding a baby,
- ➢ if you are allergic to budesonide or any other orally inhaled corticosteroid.

In some circumstances, this medicine may not be suitable and your doctor may wish to give you a different medicine. Make sure that your doctor knows what other medicines you are taking.

USING YOUR PULMICORT TURBUHALER

- ➢ Follow the instructions shown on the other side. If you have any problems, tell your doctor or pharmacist.
- ➢ It is important that you inhale each dose as directed by your doctor. The pharmacy label will usually tell you what dose to take and how often. If it doesn't, or you are not sure, ask your doctor or pharmacist.

DOSAGE

- ➢ Use as directed by your doctor.
- ➢ It is **VERY IMPORTANT** that you follow your doctor's instructions as to how many inhalations to take and how often to use your Pulmicort Turbuhaler.
- ➢ **DO NOT** inhale more doses or use your Pulmicort Turbuhaler more often than your doctor advises.
- ➢ It may take 1 to 2 weeks or longer before you feel maximum improvement, so **IT IS VERY IMPORTANT THAT YOU USE PULMICORT TURBUHALER REGULARLY. DO NOT STOP TREATMENT OR REDUCE YOUR DOSE EVEN IF YOU ARE FEELING BETTER,** unless told to do so by your doctor.
- ➢ If you miss a dose, just take your regularly scheduled next dose when it is due. **DO NOT DOUBLE** the dose.

PULMICORT TURBUHALER will often permit control of asthma symptoms with less suppression of HPA function than therapeutically equivalent oral doses of prednisone. Since budesonide is absorbed into the circulation and can be systemically active at higher doses, the full beneficial effects of PULMICORT TURBUHALER in minimizing HPA dysfunction may be expected only when recommended dosages are not exceeded and individual patients are titrated to the lowest effective dose. Since individual sensitivity to effects on cortisol production exists, physicians should consider this information when prescribing PULMICORT TURBUHALER.

Because of the possibility of systemic absorption of inhaled corticosteroids, patients treated with these drugs should be observed carefully for any evidence of systemic corticosteroid effects. Particular care should be taken in observing patients postoperatively or during periods of stress for evidence of inadequate adrenal response.

It is possible that systemic corticosteroid effects such as hypercorticism and adrenal suppression may appear in a small number of patients, particularly at higher doses. If such changes occur, PULMICORT TURBUHALER should be reduced slowly, consistent with accepted procedures for management of asthma symptoms and for tapering of systemic steroids.

A reduction of growth velocity in children or teenagers may occur as a result of inadequate control of chronic diseases such as asthma or from use of corticosteroids for treatment. Physicians should closely follow the growth of adolescents taking corticosteroids by any route and weigh the benefits of corticosteroid therapy and asthma control against the possibility of growth suppression if an adolescent's growth appears slowed.

Although patients in clinical trials have received PULMICORT TURBUHALER on a continuous basis for periods of 1 to 2 years, the long-term local and systemic effects of PULMICORT TURBUHALER in human subjects are not completely known. In particular, the effects resulting from chronic use of PULMICORT TURBUHALER on developmental or immunological processes in the mouth, pharynx, trachea, and lung are unknown.

In clinical trials with PULMICORT TURBUHALER, localized infections with Candida albicans occurred in the mouth and pharynx in some patients. If oropharyngeal candidiasis develops, it should be treated with appropriate local or systemic (i.e., oral) antifungal therapy while still continuing with PULMICORT TURBUHALER therapy, but at times therapy with PULMICORT TURBUHALER may need to be temporarily interrupted under close medical supervision.

Inhaled corticosteroids should be used with caution, if at all, in patients with active or quiescent tuberculosis infection of the respiratory tract, untreated systemic fungal, bacterial, viral or parasitic infections; or ocular herpes simplex.

Rare instances of glaucoma, increased intraocular pressure, and cataracts have been reported following the inhaled administration of corticosteroids.

Information for Patients: For proper use of PULMICORT TURBUHALER and to attain maximum improvement, the patient should read and follow the accompanying Patient's Instructions for Use carefully. In addition, patients being treated with PULMICORT TURBUHALER should receive the following information and instructions. This information is intended to aid the patient in the safe and effective use of the medication. It is not a disclosure of all possible adverse or intended effects.

- Patients should take the medication as directed and use PULMICORT TURBUHALER at regular intervals twice daily since its effectiveness depends on regular use. The patient should not alter the prescribed dosage unless advised to do so by the physician.
- PULMICORT TURBUHALER is not a bronchodilator and is not intended to treat acute or life-threatening episodes of asthma.
- PULMICORT TURBUHALER must be in the upright position (mouthpiece on top) during loading in order to provide the correct dose. PULMICORT TURBUHALER must be primed when the unit is used for the very first time. To prime the unit, hold the unit in an upright position and turn the brown grip fully to the right, then fully to the left until it clicks. Repeat. The unit is now primed and ready to load the first dose by turning the grip fully to the right and fully to the left until it clicks.

  On subsequent uses, it is not necessary to prime the unit. However, it must be loaded in the upright position immediately prior to use. Turn the brown grip fully to the right, then fully to the left until it clicks. During inhalation, PULMICORT TURBUHALER must be held in the upright (mouthpiece up) or horizontal position. Do not shake the inhaler. Place the mouthpiece between lips and inhale forcefully and deeply. The powder is then delivered to the lungs.
- Patients should not exhale through PULMICORT TURBUHALER.
- Due to the small volume of powder, the patient may not taste or sense the presence of any medication entering the lungs when inhaling from TURBUHALER. This lack of "sensation" does not indicate that the patient is not receiving benefit from PULMICORT TURBUHALER.
- Rinsing the mouth with water without swallowing after each dosing may decrease the risk of the development of oral candidiasis.
- When there are 20 doses remaining in PULMICORT TURBUHALER, a red mark will appear in the indicator window.
- PULMICORT TURBUHALER should not be used with a spacer.
- The mouthpiece should not be bitten or chewed.
- The cover should be replaced securely after each opening.
- Keep PULMICORT TURBUHALER clean and dry at all times.
- Improvement in asthma control following inhalation of PULMICORT TURBUHALER can occur within 24 hours of beginning treatment although maximum benefit may not be achieved for 1 to 2 weeks, or longer. If symptoms do not improve in that time frame, or if the condition worsens, the patient should be instructed to contact the physician.
- Patients should be warned to avoid exposure to chicken pox or measles and if they are exposed, to consult their physicians without delay.
- For proper use of PULMICORT TURBUHALER and to attain maximum improvement, the patient should read and follow the accompanying Patient's Instructions for Use.

Drug Interactions: In clinical studies, concurrent administration of budesonide and other drugs commonly used in the treatment of asthma has not resulted in an increased frequency of adverse events. Ketoconazole, a potent inhibitor of cytochrome P450 3A, may increase plasma levels of budesonide during concomitant dosing. The clinical significance of concomitant administration of ketoconazole with PULMICORT TURBUHALER is not known, but caution may be warranted.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies were conducted in mice and rats using oral administration to evaluate the carcinogenic potential of budesonide.

There was no evidence of a carcinogenic effect when budesonide was administered orally for 91 weeks to mice at doses up to 200 mcg/kg/day (approximately ½ the maximum recommended human daily inhalation dose on a mcg/m² basis).

In a 104-week carcinogenicity study in Sprague-Dawley rats, a statistically significant increase in the incidence of gliomas was observed in male rats receiving oral doses of 50 mcg/kg/day (approximately ¼ the maximum recommended human daily inhalation dose on a mcg/m² basis); no such changes were seen in male rats receiving oral doses of 10 and 25 mcg/kg/day (approximately 1/20 and 1/8 the maximum recommended human daily inhalation dose on a mcg/m² basis) or in female rats at oral doses up to 50 mcg/kg/day (approximately ¼ the maximum recommended human daily inhalation dose on a mcg/m² basis).

Two additional 104-week carcinogenicity studies have been performed with oral budesonide at doses of 50 mcg/kg/day (approximately ¼ the maximum recommended human daily inhalation dose on a mcg/m² basis) in male Sprague-Dawley and Fischer rats. These studies did not demonstrate an increased glioma incidence in budesonide-treated animals as compared with concurrent controls or reference corticosteroid-treated groups (prednisolone and triamcinolone acetonide). Compared with concurrent controls, a statistically significant increase in the incidence of hepatocellular tumors was observed in all three steroid groups

The incidence of common adverse events is based upon double-blind, placebo-controlled US clinical trials in which 1,116 adult and pediatric patients age 6-70 years (472 females and 644 males) were treated with PULMICORT TURBUHALER (200 to 800 mcg twice daily for 12 to 20 weeks) or placebo.

The following table shows the incidence of adverse events in patients previously receiving bronchodilators and/or inhaled corticosteroids in US controlled clinical trials. This population included 232 male and 62 female pediatric patients (age 6 to 17 years) and 332 male and 331 female adult patients (age 18 years and greater).

Adverse Events with ≥ 3% Incidence reported by Patients on PULMICORT TURBUHALER

Adverse Event	Placebo N=284 %	PULMICORT TURBUHALER 200 mcg twice daily N=286 %	400 mcg twice daily N=289 %	800 mcg twice daily N=98 %
Respiratory System				
Respiratory infection	17	20	24	19
Pharyngitis	9	10	9	5
Sinusitis	7	11	7	2
Voice alteration	0	1	2	6
Body As A Whole				
Headache	7	14	13	14
Flu syndrome	6	6	6	14
Pain	2	5	5	5
Back pain	1	2	3	6
Fever	2	2	4	0
Digestive System				
Oral candidiasis	2	2	4	4
Dyspepsia	2	1	2	4
Gastroenteritis	1	1	2	3
Nausea	2	2	1	3
Average Duration of Exposure (days)	59	79	80	80

The table above includes all events (whether considered drug-related or non drug-related by the investigators) that occurred at a rate of ≥3% in any one PULMICORT TURBUHALER group and were more common than in the placebo group. In considering these data, the increased average duration of exposure for PULMICORT TURBUHALER patients should be taken into account.

The following other adverse events occurred in these clinical trials using PULMICORT TURBUHALER with an incidence of 1 to 3% and were more common on PULMICORT TURBUHALER than on placebo:

Body As A Whole: neck pain
Cardiovascular: syncope
Digestive: abdominal pain, dry mouth, vomiting
Metabolic and Nutritional: weight gain
Musculoskeletal: fracture, myalgia
Nervous: hypertonia, migraine
Platelet, Bleeding and Clotting: ecchymosis
Psychiatric: insomnia
Resistance Mechanisms: infection
Special Senses: taste perversion

In a 20-week trial in adult asthmatics who previously required oral corticosteroids, the effects of PULMICORT TURBUHALER 400 mcg twice daily (N=53) and 800 mcg twice daily (N=53) were compared with placebo (N=53) on the frequency of reported adverse events. Adverse events, whether considered drug-related or non drug-related by the investigators, reported in more than five patients in the PULMICORT TURBUHALER group and which occurred more frequently with PULMICORT TURBUHALER than placebo are shown below (% PULMICORT TURBUHALER and % placebo). In considering these data, the increased average duration of exposure for PULMICORT TURBUHALER patients (78 days for PULMICORT TURBUHALER vs. 41 days for placebo) should be taken into account.

Body As A Whole: asthenia (9% and 2%)
headache (12% and 2%)
pain (10% and 2%)
Digestive: dyspepsia (8% and 0%)
nausea (6% and 0%)
oral candidiasis (10% and 0%)
Musculoskeletal: arthralgia (5% and 0%)
Respiratory: cough increased (6% and 2%)
respiratory infection (32% and 13%)
rhinitis (6% and 2%)
sinusitis (16% and 11%)

Pediatric Studies: In a 12-week placebo-controlled trial in 404 pediatric patients 6 to 18 years of age previously maintained on inhaled corticosteroids, the frequency of adverse events for each age category (6 to 12 years, 13 to 18 years) was comparable for PULMICORT TURBUHALER (at 100, 200 and 400 mcg twice daily) and placebo. There were no clinically relevant differences in the pattern or severity of adverse events in children compared with those reported in adults.

Adverse Event Reports From Other Sources: Rare adverse events reported in the published literature or from marketing experience include: immediate and delayed hypersensitivity reactions including: rash, contact dermatitis, urticaria, angioedema and bronchospasm; symptoms of hypocorticism and hypercorticism; psychiatric symptoms including depression, aggressive reactions, irritability, anxiety and psychosis.

OVERDOSAGE

The potential for acute toxic effects following overdose of PULMICORT TURBUHALER is low. If used at excessive doses for prolonged periods, systemic corticosteroid effects such as hypercorticism may occur (see PRECAUTIONS). PULMICORT TURBUHALER at twice the highest recommended dose (1200 mcg daily) administered for 6 weeks caused a significant reduction (27%) in the plasma cortisol response to a 6-hour infusion of ACTH compared with placebo (+1%). The corresponding effect of 10 mg prednisone daily was a 35% reduction in the plasma cortisol response to ACTH.

The minimal inhalation lethal dose in mice was 100 mg/kg (approximately 250 times the maximum recommended human daily inhalation dose on a mcg/m² basis). There were no deaths following the administration of an inhalation dose of 68 mg/kg in rats (approximately 345 times the maximum recommended human daily inhalation dose on a mcg/m² basis). The minimal oral lethal dose was 200 mg/kg in mice and less than 100 mg/kg in rats (approximately 500 times the maximum recommended human daily inhalation dose based on a mcg/m² basis).

DOSAGE AND ADMINISTRATION

PULMICORT TURBUHALER should be administered by the orally inhaled route in asthmatic patients age 6 years and older. Individual patients will experience a variable onset and degree of symptom relief. Generally, PULMICORT TURBUHALER has a relatively rapid onset of action for an inhaled corticosteriod. Improvement in asthma control following inhaled administration of PULMICORT TURBUHALER can occur within 24 hours of initiation of treatment, although maximum benefit may not be achieved for 1 to 2 weeks, or longer. The safety and efficacy of PULMICORT TURBUHALER when administered in excess of recommended doses have not been established.

(budesonide, prednisolone, triamcinolone acetonide) in these studies.

The mutagenic potential of budesonide was evaluated in six different test systems; Ames Salmonella/microsome plate test, mouse micronucleus test, mouse lymphoma test, chromosome aberration test in human lymphocytes, sex-linked recessive lethal test in Drosophila melanogaster, and DNA repair analysis in rat hepatocyte culture. Budesonide was not mutagenic or clastogenic in any of these tests.

The effect of subcutaneous budesonide on fertility and general reproductive performance was studied in rats. At 20 mcg/kg/day (approximately $^1/_{10}$ the maximum recommended human daily inhalation dose on a mcg/m² basis), decreases in maternal body weight gain, prenatal viability, and viability of the young at birth and during lactation were observed. No such effects were noted at 5 mcg/kg (approximately $^1/_{40}$ the maximum recommended human daily inhalation dose on a mcg/m² basis).

Pregnancy: Teratogenic Effects: Pregnancy Category C: As with other glucocorticoids, budesonide produced fetal loss, decreased pup weight and skeletal abnormalities at subcutaneous doses of 25 mcg/kg/day (approximately $^1/_4$ the maximum recommended human daily inhalation dose on a mcg/m² basis) in rabbits and 500 mcg/kg/day (approximately $2^1/_2$ times the maximum recommended human daily inhalation dose on a mcg/m² basis) in rats.

No teratogenic or embryocidal effects were observed in rats when budesonide was administered by inhalation at doses of 100 to 250 mcg/kg/day (approximately $^1/_2$ to $1^1/_4$ times the maximum recommended human daily inhalation dose on a mcg/m² basis).

There are no adequate and well-controlled studies in pregnant women. Budesonide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Experience with oral corticosteroids since their introduction in pharmacologic as opposed to physiologic doses suggests that rodents are more prone to teratogenic effects from corticosteroids than humans.

Nonteratogenic Effects: Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully observed.

Nursing Mothers: Corticosteroids are secreted in human milk. Because of the potential for adverse reactions in nursing infants from any corticosteroid, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother. Actual data for budesonide are lacking.

Pediatric Use: Safety and effectiveness of PULMICORT TURBUHALER in pediatric patients below 6 years of age have not been established.

In pediatric asthma patients the frequency of adverse events observed with PULMICORT TURBUHALER was similar between the 6- to 12-year age group (N=172) compared with the 13- to 17-year age group (N=124).

Oral corticosteroids have been shown to cause growth suppression in pediatric and adolescent patients, particularly with higher doses over extended periods. If a pediatric or adolescent patient on any corticosteroid appears to have growth suppression, the possibility that they are particularly sensitive to this effect of corticosteroids should be considered (see PRECAUTIONS).

Geriatric Use: One hundred patients 65 years or older were included in the US and non-US controlled clinical trials of PULMICORT TURBUHALER. There were no differences in the safety and efficacy of the drug compared to those seen in younger patients.

ADVERSE REACTIONS

The following adverse reactions were reported in patients treated with PULMICORT TURBUHALER.

The recommended starting dose and the highest recommended dose of PULMICORT TURBUHALER, based on prior asthma therapy, are listed in the following table.

	Previous Therapy	Recommended Starting Dose	Highest Recommended Dose
Adults:	Bronchodilators alone	200 to 400 mcg twice daily	400 mcg twice daily
	Inhaled Corticosteroids	200 to 400 mcg twice daily	800 mcg twice daily
	Oral Corticosteroids	400 to 800 mcg twice daily	800 mcg twice daily
Children:	Bronchodilators alone	200 mcg twice daily	400 mcg twice daily
	Inhaled Corticosteroids	200 mcg twice daily	400 mcg twice daily
	Oral Corticosteroids	The highest recommended dose in children is 400 mcg twice daily	

Patients Maintained on Chronic Oral Corticosteroids

Initially, PULMICORT TURBUHALER should be used concurrently with the patient's usual maintenance dose of systemic corticosteroid. After approximately one week, gradual withdrawal of the systemic corticosteroid is started by reducing the daily or alternate daily dose. The next reduction is made after an interval of one or two weeks, depending on the response of the patient. Generally, these decrements should not exceed 2.5 mg of prednisone or its equivalent. A slow rate of withdrawal is strongly recommended. During reduction of oral corticosteroids, patients should be carefully monitored for asthma instability, including objective measures of airway function, and for adrenal insufficiency (see WARNINGS). During withdrawal, some patients may experience symptoms of systemic corticosteroid withdrawal, e.g., joint and/or muscular pain, lassitude and depression, despite maintenance or even improvement in pulmonary function. Such patients should be encouraged to continue with PULMICORT TURBUHALER but should be monitored for objective signs of adrenal insufficiency. If evidence of adrenal insufficiency occurs, the systemic corticosteroid doses should be increased temporarily and thereafter withdrawal should continue more slowly. During periods of stress or a severe asthma attack, transfer patients may require supplementary treatment with systemic corticosteroids.

NOTE: In all patients it is desirable to titrate to the lowest effective dose once asthma stability is achieved.

Patients should be instructed to prime PULMICORT TURBUHALER prior to its initial use, and instructed to inhale deeply and forcefully each time the unit is used. Rinsing the mouth after inhalation is also recommended.

Directions for Use: Illustrated Patient's Instructions for Use accompany each package of PULMICORT TURBUHALER.

HOW SUPPLIED

PULMICORT TURBUHALER consists of a number of assembled plastic details, the main parts being the dosing mechanism, the storage unit for drug substance and the mouthpiece. The inhaler is protected by a white outer tubular cover screwed onto the inhaler. The body of the inhaler is white and the turning grip is brown. The following wording is printed on the grip in raised lettering, "budesonide 200." TURBUHALER cannot be refilled and should be discarded when empty.

PULMICORT TURBUHALER is available as 200 mcg/dose, 200 doses.

Store at controlled room temperature 20°C to 25°C (68°F to 72°F) [see USP].

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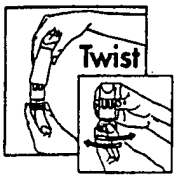
HOW TO USE YOUR PULMICORT TURBUHALER

Read the complete instructions carefully and use only as directed.

BEFORE YOU USE A NEW PULMICORT TURBUHALER

Before you use a new Pulmicort Turbuhaler for the first time, you should prime it. To do this, turn the cover and lift off. Hold Pulmicort Turbuhaler upright (with mouthpiece up), then twist the brown grip fully to the right and back again to the left. Repeat. Now you are ready to use it. **You do not have to prime it any other time after this, even if you put it aside for a prolonged period of time.**

FOLLOW THE INSTRUCTIONS BELOW:

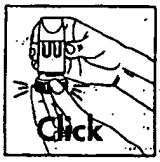


1 LOADING A DOSE

➤ Twist the cover and lift off.

➤ In order to provide the correct dose, Pulmicort Turbuhaler must be held in the upright position (mouthpiece up) whenever a dose of medication is being loaded.

➤ Twist the brown grip fully to the right as far as it will go. Twist it back again fully to the left.



➤ You will hear a click.

➤ Turn your head away from the inhaler and breathe out. Do not blow or exhale into the inhaler. Do not shake the inhaler after loading it.

2 INHALING THE DOSE

➤ When you are inhaling, Pulmicort Turbuhaler must be held in the upright (mouthpiece up) or horizontal position.

➤ Place the mouthpiece between your lips and inhale deeply and forcefully.

➤ If more than one dose is required, just repeat the steps above.

➤ When you are finished, place the cover back on the inhaler and twist shut. Rinse your mouth with water. Do not swallow.

➤ Keep your Pulmicort Turbuhaler clean and dry at all times.

STORING YOUR PULMICORT TURBUHALER

➤ After each use, place the white cover back on and twist it firmly into place.

➤ Keep Pulmicort Turbuhaler in a dry place at controlled room temperature, 68° to 77°F (20° to 25°C).

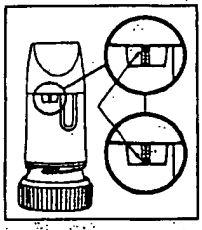
➤ Keep your Pulmicort Turbuhaler out of the reach of young children.

➤ DO NOT use after the date shown on the body of your Turbuhaler.

HOW TO KNOW WHEN YOUR PULMICORT TURBUHALER IS EMPTY

THERE ARE 200 DOSES IN EACH PULMICORT TURBUHALER.

Your Pulmicort Turbuhaler has a convenient dose indicator window just below the mouthpiece.



➤ When a red mark appears at the top of the window, there are 20 doses of medicine remaining. Now is the time to get your next Pulmicort Turbuhaler.

➤ When the red mark reaches the bottom of the window, your inhaler is empty. Discard it. (You may still hear a sound if you shake it—this sound is not the medicine. This sound is produced by the drying agent inside Turbuhaler.)

➤ Do not immerse it in water to find out if it is empty. Simply check your dose indicator window.

FURTHER INFORMATION ABOUT PULMICORT TURBUHALER

➤ Pulmicort Turbuhaler delivers your medicine as a very fine powder that you may not taste, smell, or feel. By following the instructions for use in this leaflet, you can be confident that you have received the correct dose.

➤ Pulmicort Turbuhaler should not be used with a spacer.

➤ Pulmicort Turbuhaler contains only budesonide and does not contain any inactive ingredients.

➤ Pulmicort Turbuhaler is specially designed to deliver only one dose at a time, no matter how often you click the brown grip. If you accidentally blow into your inhaler after loading a dose, simply follow the instructions for loading a new dose.

This leaflet does not contain the complete information about your medicine. If you have any questions, or are not sure about something, then you should ask your doctor or pharmacist.

You may want to read this leaflet again. Please DO NOT THROW IT AWAY until you have finished your medicine.

REMEMBER: This medicine has been prescribed for you by your doctor. DO NOT give this medicine to anyone else.

USE THIS PRODUCT AS DIRECTED, UNLESS INSTRUCTED TO DO OTHERWISE BY YOUR DOCTOR.

If you have further questions about the use of Pulmicort Turbuhaler, call:

1-800-343-4777

ASTRA Astra USA, Inc., Westborough, MA 01581

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Symbicort® Turbuhaler® 80/4.5µg/dose
Symbicort® Turbuhaler® 160/4.5µg/dose

budesonide/formoterol

Inhalation powder

Composition

Each delivered dose (the dose that leaves the mouthpiece) contains as active constituents:
budesonide 80 micrograms/inhalation and formoterol fumarate dihydrate 4.5 micrograms/inhalation respectively budesonide 160 micrograms/inhalation and formoterol fumarate dihydrate 4.5 micrograms/inhalation.

Symbicort Turbuhaler 80/4.5 micrograms/inhalation delivers the same amount of budesonide and formoterol as the corresponding Turbuhaler monoproducts, i.e. budesonide 100 micrograms/inhalation (metered dose) and formoterol 6 micrograms/inhalation (metered dose) alternatively labelled as 4.5 micrograms/inhalation (delivered dose).

Symbicort Turbuhaler 160/4.5 micrograms/inhalation delivers the same amount of budesonide and formoterol as the corresponding Turbuhaler monoproducts, i.e. budesonide 200 micrograms/ inhalation (metered dose) and formoterol 8 micrograms/inhalation (metered dose) alternatively labelled as 4.5 micrograms/inhalation (delivered dose).

Indication

Symbicort Turbuhaler is indicated in the regular treatment of asthma where use of a combination (inhaled corticosteroid and long acting beta-agonist) is appropriate:

- patients not adequately controlled with inhaled corticosteroids and "as needed" inhaled short acting $beta_2$-agonists.

or

- patients already adequately controlled on both inhaled corticosteroids and long acting $beta_2$-agonists.

Note: Symbicort (80/4.5 micrograms/inhalation) is not appropriate in patients with severe asthma.

Dosage and method of administration

Symbicort Turbuhaler is not intended for the initial management of asthma. The dosage of the components of Symbicort Turbuhaler is individual and should be adjusted to the severity of the disease. This should be considered when treatment with combination products is initiated. If an individual patient should require dosages outside the recommended regimen, appropriate doses of beta-agonist and/or corticosteroids should be prescribed.

Patients should be regularly reassessed by a doctor, so that the dosage of Symbicort Turbuhaler remains optimal. The dose should be titrated to the lowest dose at which effective control of symptoms is maintained. When control of symptoms is maintained with the lowest recommended dosage, then the next step could include a test of inhaled corticosteroid alone.

Recommended doses:
Adults and adolescents (12 years and older):
Symbicort Turbuhaler 80/4.5 micrograms/dose 1-2 inhalations twice daily.
Symbicort Turbuhaler 160/4.5 micrograms/dose 1-2 inhalations twice daily.

In usual practice when control of symptoms is achieved with the twice daily regimen, titration to the lowest effective dose could include Symbicort Turbuhaler given once daily.

Children under 12 years: Efficacy and safety have not been fully studied in children. Symbicort is not recommended for children under 12 years of age.

Special patient groups: There is no need to adjust the dose in elderly patients. There are no data available for use of Symbicort Turbuhaler in patients with hepatic or renal impairment. As budesonide and formoterol are primarily eliminated via hepatic

Concomitant treatment with ketoconazole or other potent CYP3A4 inhibitors should be avoided. If this is not possible the time interval between administration of the interacting drugs should be as long as possible.

Symbicort Turbuhaler should be administered with caution in patients with thyrotoxicosis, phaeochromocytoma, diabetes mellitus, untreated hypokalaemia, hypertrophic obstructive cardiomyopathy, idiopathic subvalvular aortic stenosis, severe hypertension, aneurysm or other severe cardiovascular disorders, such as ischaemic heart disease, tachyarrhythmias or severe heart failure.

Caution should be observed when treating patients with prolongation of the QTc-interval. Formoterol itself may induce prolongation of the QTc-interval.

Potentially serious hypokalaemia may result from high doses of $beta_2$-agonists. Concomitant treatment with drugs which can induce hypokalaemia may add to a possible hypokalaemic effect from high doses of a $beta_2$-agonist. Particular caution is recommended in acute severe asthma as the associated risk may be augmented by hypoxia. The hypokalaemic effect may be potentiated by concomitant treatment with xanthine-derivatives, steroids and diuretics. It is recommended that serum potassium levels are monitored during treatment of acute severe asthma.

As for all $beta_2$-agonists, additional blood glucose controls should be considered in diabetic patients.

Symbicort Turbuhaler contains lactose (<1 mg/inhalation). This amount does not normally cause problems in lactose intolerant people.

Interactions

Ketoconazole 200 mg once daily increased plasma levels of concomitantly administered oral budesonide (single dose of 3 mg), on average six-fold. When ketoconazole was administered 12 hours after budesonide the concentration was on average increased three-fold. Information about this interaction is lacking for inhaled budesonide, but marked increases in plasma levels could be expected. Since data to give dosage recommendations are lacking, the combination should be avoided. If this is not possible the time interval between administration of ketoconazole and budesonide should be as long as possible. A reduction in the dose of budesonide should also be considered. Other potent inhibitors of CYP3A4 are also likely to markedly increase plasma levels of budesonide.

Beta-adrenergic blockers can weaken or inhibit the effect of formoterol. Symbicort Turbuhaler should therefore not be given together with beta-adrenergic blockers (including eye drops) unless there are compelling reasons.

Concomitant treatment with quinidine, disopyramide, procainamide, phenothiazines, antihistamines (terfenadine), monoamine oxidase inhibitors and tricyclic antidepressives can prolong the QTc-interval and increase the risk of ventricular arrhythmias.

In addition L-Dopa, L-thyroxine, oxytocin and alcohol can impair cardiac tolerance towards β_2-sympathomimetics.

Concomitant treatment with monoamine oxidase inhibitors including agents with similar properties such as furazolidone and procarbazine may precipitate hypertensive reactions.

There is an elevated risk of arrhythmias in patients receiving concomitant anaesthesia with halogenated hydrocarbons.

Concomitant use of other beta-adrenergic drugs can have a potentially additive effect.

Hypokalaemia may increase the disposition towards arrhythmias in patients who are treated with digitalis glycosides.

Budesonide has not been observed to interact with any other drugs

metabolism, an increased exposure can be expected in patients with severe liver cirrhosis.

Instructions for correct use of Turbuhaler:
Turbuhaler is inspiratory flow-driven, which means that when the patient inhales through the mouthpiece, the substance will follow the inspired air into the airways.

Note: It is important to instruct the patient
- To carefully read the instructions for use in the patient information leaflet which is packed together with each inhaler
- To breathe in forcefully and deeply through the mouthpiece to ensure that an optimal dose is delivered to the lungs
- Never to breathe out through the mouthpiece
- To rinse the mouth out with water after inhaling the prescribed dose to minimise the risk of oropharyngeal thrush

The patient may not taste or feel any medication when using Turbuhaler due to the small amount of drug dispensed.

Contra-indications
Hypersensitivity to budesonide, formoterol or inhaled lactose.

Special warnings and precautions for use
It is recommended that the dose is tapered when the treatment is discontinued.

D If patients find the treatment ineffective, or exceed the current dose of the fixed combination, medical attention must be sought.

E Increasing use of rescue bronchodilators indicates a worsening of the underlying condition and warrants a reassessment of the asthma therapy. Sudden and progressive deterioration in control of asthma is potentially life threatening and the patient should undergo urgent medical assessment. In this situation consideration should be given to the need for increased therapy with corticosteroids or addition of systemic anti-inflammatory therapy, such as a course of oral corticosteroids, or antibiotic treatment if an infection is present.

There are no data available on the use of Symbicort Turbuhaler in the treatment of an acute asthma attack. Patients should be advised to have their rescue medication available at all times.

Therapy should not be initiated during an exacerbation.

As with other inhalation therapy, paradoxical bronchospasm may occur, with an immediate increase in wheezing after dosing. If a severe reaction occurs, treatment should be re-assessed and alternative therapy instituted if necessary.

Systemic effects may occur with any inhaled corticosteroid, particularly at high doses prescribed for long periods. These effects are much less likely to occur with inhalation treatment than with oral corticosteroids. Possible systemic effects include adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract and glaucoma. It is important, therefore, that the dose of inhaled corticosteroid is adjusted to the lowest dose at which effective control is maintained.

Physicians should closely follow the growth of children and adolescents taking long term corticosteroids by any route, and weigh the benefits of the corticosteroid therapy against the possible risk of growth suppression.

If there is any reason to suppose that adrenal function is impaired from previous systemic steroid therapy, care should be taken when transferring patients to Symbicort Turbuhaler therapy.

The benefits of inhaled budesonide therapy would normally minimise the need for oral steroids, but patients transferring from oral steroids may remain at risk of impaired adrenal reserve for a considerable time. Patients who have required high dose emergency corticosteroid therapy in the past may also be at risk. This possibility of residual adrenal impairment should always be borne in mind in emergency and elective situations likely to produce stress, and appropriate corticosteroid treatment must be considered. The extent of the adrenal impairment may require specialist advice before elective procedures.

To minimise the risk of oropharyngeal candida infection the patient should be instructed to rinse the mouth with water after each dosing occasion.

used in the treatment of asthma.

Pregnancy and lactation
For Symbicort Turbuhaler or the concomitant treatment with formoterol and budesonide, no clinical data on exposed pregnancies are available. Animal studies with respect to reproductive toxicity of the combination have not been performed.

There are no adequate data from use of formoterol in pregnant women. In animal studies formoterol has caused adverse effects in reproduction studies at very high systemic exposure levels.

Data on approximately 2000 exposed pregnancies indicate no increased teratogenic risk associated with the use of inhaled budesonide. In animal studies glucocorticosteroids have been shown to induce malformations. This is not likely to be relevant for humans given recommended doses.

Animal studies have also identified an involvement of excess prenatal glucocorticoids in increased risks for intrauterine growth retardation, adult cardiovascular disease and permanent changes in glucocorticoid receptor density, neurotransmitter turnover and behaviour at exposures below the teratogenic dose range.

During pregnancy, Symbicort Turbuhaler should only be used when the benefits outweigh the potential risks. The lowest effective dose of budesonide needed to maintain adequate asthma control should be used.

It is not known whether formoterol or budesonide passes into human breast milk. In rats, small amounts of formoterol have been detected in maternal milk. Administration of Symbicort Turbuhaler to women who are breastfeeding should only be considered if the expected benefit to the mother is greater than any possible risk to the child.

Effects on ability to drive and use machines
Symbicort Turbuhaler does not affect the ability to drive or use machines.

Undesirable effects
Since Symbicort Turbuhaler contains both budesonide and formoterol, the same pattern of undesirable effects as reported for these substances may occur. No increased incidence of adverse reactions has been seen following concurrent administration of the two compounds. The most common drug related adverse reactions are pharmacologically predictable side-effects of beta$_2$-agonist therapy, such as tremor and palpitations. These tend to be mild and usually disappear within a few days of treatment.

Adverse reactions, which have been associated with budesonide or formoterol, are given below.

Common (>1/100)	*Central nervous system:*	Headache
	Cardiovascular system:	Palpitations
	Musculoskeletal system:	Tremor
	Respiratory tract:	Candida infections in the oropharynx, mild irritation in the throat, coughing, hoarseness
Uncommon	*Cardiovascular system:*	Tachycardia
	Musculoskeletal system:	Muscle cramps
	Central nervous system:	Agitation, restlessness, nervousness, nausea, dizziness, sleep disturbances
Rare (<1/1000)	*Skin:*	Exanthema, urticaria, pruritus
	Respiratory tract:	Bronchospasm

Very rare undesirable effects, some of which are of a potentially serious nature include:

Budesonide: Psychiatric symptoms such as depression, behavioural disturbances (mainly in children), signs or symptoms of systemic glucocorticosteroid effects (including hypofunction of the adrenal gland), immediate or delayed hypersensitivity reactions (including dermatitis, angioedema and bronchospasm), bruising.

Patient's Instructions for Use

ADVAIR DISKUS® 100/50, 250/50, 500/50

(fluticasone propionate 100, 250, 500 mcg and salmeterol* 50 mcg inhalation powder)

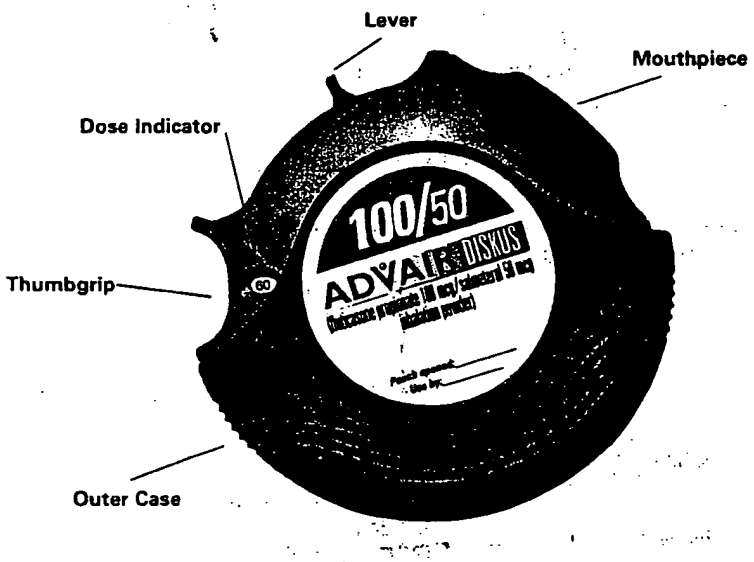
ADVAIR DISKUS® 100/50
(fluticasone propionate 100 mcg and salmeterol* 50 mcg inhalation powder)

ADVAIR DISKUS® 250/50
(fluticasone propionate 250 mcg and salmeterol* 50 mcg inhalation powder)

ADVAIR DISKUS® 500/50
(fluticasone propionate 500 mcg and salmeterol* 50 mcg inhalation powder)

***As salmeterol xinafoate salt 72.5 mcg, equivalent to salmeterol base 50 mcg**

FOR ORAL INHALATION ONLY



Read this leaflet carefully before you start to take your medicine. It provides a summary of information about your medicine. Keep it for future use. Read the leaflet every time you refill your prescription because there may be new information.

For more information ask your doctor or pharmacist.

What Is ADVAIR DISKUS®?

Your doctor has prescribed ADVAIR DISKUS 100/50, ADVAIR DISKUS 250/50, or ADVAIR DISKUS 500/50. The medicine is available in 3 different strengths, and your doctor has chosen the one most suitable for you.

Asthma is a long-term condition affecting the lungs. Symptoms of asthma include shortness of breath, wheezing, chest tightness, and cough. Two main causes of asthma

ADVAIR DISKUS contains 2 medicines, fluticasone propionate and salmeterol xinafoate, which treat these 2 causes of asthma symptoms. Fluticasone propionate is a synthetic corticosteroid. Corticosteroids are natural anti-inflammatory substances found in the body. They are used to treat asthma because they reduce airway inflammation.

Salmeterol is a long-acting bronchodilator that helps prevent and relieve bronchospasm, making it easier to breathe.

When inhaled regularly, ADVAIR DISKUS helps to prevent symptoms of asthma.

Important Points to Remember About Using ADVAIR DISKUS

1. **TELL YOUR DOCTOR BEFORE STARTING TO TAKE THIS MEDICINE:**
   - if you are pregnant (or intending to become pregnant),
   - if you are breastfeeding a baby,
   - if you are allergic to ADVAIR DISKUS, any other medicines, or food products. In some circumstances, this medicine may not be suitable and your doctor may wish to give you a different medicine.
   - Make sure that your doctor knows what other medicines you are taking.
2. It is important that you inhale each dose as your doctor has advised. The label will usually tell you what dose to take and how often. If it doesn't, or if you are not sure, ask your doctor or pharmacist. **Do not use ADVAIR DISKUS more frequently than 2 times daily, morning and evening, approximately 12 hours apart, at the recommended dose of 1 inhalation each time.**
3. ADVAIR DISKUS delivers your dose of medicine as a very fine powder **that most, but not all, patients can taste or feel.** Whether or not you are able to taste or feel your dose of medicine, you should not exceed the recommended dose of 1 inhalation each morning and evening, approximately 12 hours apart. If you are not sure you are receiving your dose of ADVAIR DISKUS, contact your doctor or pharmacist.
4. You may feel better after the first dose of ADVAIR DISKUS; however, it may take 1 week or longer to achieve maximum benefit. It is **IMPORTANT THAT YOU USE ADVAIR DISKUS REGULARLY. DO NOT STOP TREATMENT EVEN IF YOU ARE FEELING BETTER** unless told to do so by your doctor.
5. If you miss a dose, just take your next scheduled dose when it is due. **DO NOT DOUBLE** the dose.
6. **DO NOT USE ADVAIR DISKUS TO *RELIEVE* SUDDEN ASTHMA SYMPTOMS** (e.g., sudden severe onset or worsening of wheezing, cough, chest tightness, and/or shortness of breath that has been diagnosed by your doctor as due to asthma). **An inhaled, short-acting bronchodilator such as albuterol should be used to *relieve* sudden asthma symptoms.** If you do not have an inhaled, short-acting bronchodilator, contact your doctor to have one prescribed for you. **You should continue to take ADVAIR DISKUS as instructed by your doctor.**
7. **Tell your doctor immediately if your asthma is getting worse, as indicated by any of the following situations.**
   - Your inhaled, short-acting bronchodilator becomes less effective.
   - You need more inhalations than usual of your inhaled, short-acting bronchodilator.
   - You have a significant decrease in your peak flow measurement as previously defined by your doctor.
8. If your symptoms do not improve after using ADVAIR DISKUS regularly for 2 weeks, tell your doctor.
9. **While you are taking ADVAIR DISKUS twice daily, you should not use SEREVENT® DISKUS® (salmeterol xinafoate inhalation powder) or SEREVENT® (salmeterol xinafoate) Inhalation Aerosol for any reason, including prevention of exercise-induced asthma or the maintenance treatment of asthma.**
10. Use other inhaled medicines only as directed by your doctor.
11. Do not use ADVAIR DISKUS with a spacer device.

How to Use Your ADVAIR DISKUS®

Follow the instructions below. If you have any questions, ask your doctor or pharmacist.

When you take the ADVAIR DISKUS out of the box and foil overwrap pouch, write the **"Pouch opened"** and **"Use by"** dates on the label in the space provided on the device. **The "Use by" date is 1 month from date of opening.**

The DISKUS® inhalation device will be in the closed position when the pouch is opened.

Figure 1

The **dose indicator** on the top of the DISKUS tells you how many doses are left. The dose indicator number will decrease each time you use the DISKUS. After the DISKUS has delivered 55 doses (23 doses for the institutional or sample pack), numbers 5 to 0 will appear in **red** to warn you that there are only a few doses left *(see Figure 1)*.

Figure 2

Taking a dose of ADVAIR DISKUS requires the following 3 simple steps: Open, Click, Inhale.

1 OPEN: Hold the DISKUS in one hand and put the thumb of your other hand on the **thumbgrip**. Push your thumb away from you as far as it will go until the mouthpiece appears and snaps into position *(see Figure 2)*.

Figure 3

2 CLICK: Hold the DISKUS in a level, horizontal position with the mouthpiece towards you. Slide the **lever** away from you as far as it will go until it **clicks** *(see Figure 3)*. The DISKUS is now ready to use.

Every time the **lever** is pushed back, a dose is ready to be inhaled. This is shown by a decrease in numbers on the dose counter.

To avoid releasing or wasting doses:

- **Do not close the DISKUS.**
- **Do not tilt the DISKUS.**
- **Do not play with the lever.**
- **Do not advance the lever more than once.**

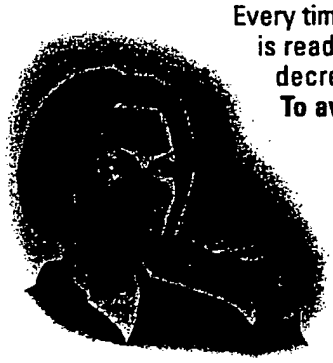


Figure 4

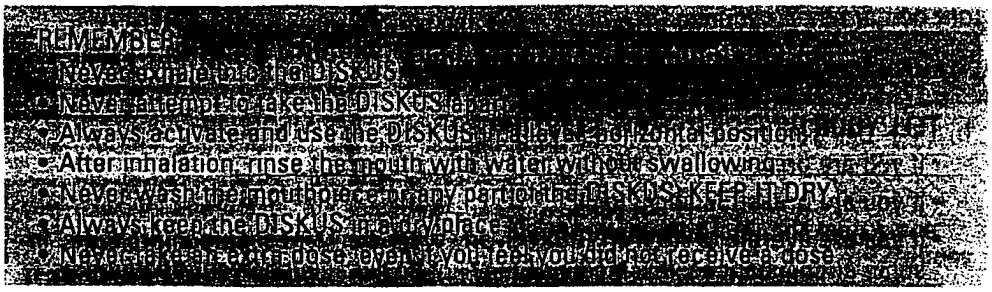
3 INHALE: Before inhaling your dose of ADVAIR DISKUS, breathe out as far as is comfortable, holding the DISKUS level and away from your mouth *(see Figure 4)*. **Remember, never breathe out into the DISKUS mouthpiece.**

Figure 5

Put the mouthpiece to your lips *(see Figure 5)*. Breathe in quickly and deeply through the DISKUS, not through your nose.

Remove the DISKUS from your mouth. Hold your breath for about 10 seconds, or for as long as is comfortable

CLOSE the DISKUS when you are finished taking a dose so that the DISKUS will be ready for you to take your next dose. Put your thumb on the thumbgrip and slide the thumbgrip back towards you as far as it will go *(see Figure 6)*. The DISKUS will click shut. The lever will automatically return to its original position. The DISKUS is now ready for you to take your next scheduled dose, due in approximately 12 hours. (Repeat steps 1 through 3.)



Storing Your ADVAIR DISKUS

Store at controlled room temperature, 20° to 25°C (68° to 77°F) in a dry place away from direct heat or sunlight. Keep out of reach of children. The DISKUS inhalation device is not reusable. The device should be discarded 1 month after removal from the moisture-protective foil overwrap pouch or after every blister has been used (when the dose indicator reads "0"), whichever comes first. Do not attempt to take the device apart.

REMEMBER: This medicine has been prescribed for you by your doctor. DO NOT give this medicine to anyone else.

Further Information

This leaflet does not contain the complete information about your medicine. *If you have any questions, or are not sure about something, then you should ask your doctor or pharmacist.*

You may want to read this leaflet again. Please DO NOT THROW IT AWAY until you have finished your medicine.

Your doctor has determined that this product is likely to help your personal health. **USE THIS PRODUCT AS DIRECTED, UNLESS INSTRUCTED TO DO OTHERWISE BY YOUR DOCTOR.** If you have any questions about alternatives, consult with your doctor.

GlaxoSmithKline
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Five Moore Drive, Research Triangle Park, NC 27709

March 2003 RL-1183 4155033

Budesonide/Formoterol Combination Therapy as Both Maintenance and Reliever Medication in Asthma

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Asthma control is improved by combining inhaled corticosteroids with long-acting β_2-agonists. However, fluctuating asthma control still occurs. We hypothesized that in patients receiving low maintenance dose budesonide/formoterol (bud/form), replacing short-acting β_2-agonist (SABA) reliever with as-needed bud/form would provide rapid symptom relief and simultaneous adjustment in antiinflammatory therapy, thereby reducing exacerbations. In this double-blind, randomized, parallel-group study, 2,760 patients with asthma aged 4–80 years (FEV_1 60–100% predicted) received either terbutaline 0.4 mg as SABA with bud/form 80/4.5 μg twice a day (bud/form + SABA) or bud 320 μg twice a day (bud + SABA) or bud/form 80/4.5 μg twice a day with 80/4.5 μg as-needed (bud/form maintenance + relief). Children used a once-nocte maintenance dose. Bud/form maintenance + relief prolonged time to first severe exacerbation ($p < 0.001$; primary endpoint), resulting in a 45–47% lower exacerbation risk versus bud/form + SABA (hazard ratio, 0.55; 95% confidence interval, 0.44, 0.67) or bud + SABA (hazard ratio, 0.53; 95% confidence interval 0.43, 0.65). Bud/form maintenance + relief also prolonged the time to the first, second, and third exacerbation requiring medical intervention ($p < 0.001$), reduced severe exacerbation rate, and improved symptoms, awakenings, and lung function compared with both fixed dosing regimens.

Keywords: inhaled corticosteroids; long-acting β_2-agonists; management; single inhaler

The combination of low or moderate doses of inhaled corticosteroids (ICS) with long-acting β_2-agonists (LABA) improves asthma control in adults and reduces exacerbations (OPTIMA study [1]; FACET study [2]); however, the evidence in pediatric patients is less compelling (3). The combination of ICS plus LABA for maintenance therapy is endorsed in asthma treatment guidelines for the treatment of moderate to severe asthma (4). Studies such as OPTIMA and FACET have led to marked improvements in asthma control using lower doses of ICS. Optimal asthma control was not achieved, however, as patients in these studies still had a notable requirement for short-acting reliever therapy or experienced exacerbations.

Periodic fluctuations in symptoms and airway inflammation are characteristics of asthma, which means that treatment requirements, especially reliever use, can vary over time. Moreover, reliever medication that provides rapid bronchodilation and symptom relief but that does not treat the underlying inflammatory process can be overrelied on (5). One possible solution could be to use a combination inhaler containing both an ICS and an LABA for both regular maintenance therapy and as needed. This strategy provides additional antiinflammatory therapy and rapid symptom relief if symptoms appear. Such an approach is possible with the combination inhaler containing budesonide and formoterol, as this combination has an onset of bronchodilator action within the first minute (6), with a similar efficacy and safety to salbutamol in patients with acute severe asthma (7).

We hypothesized that in patients already receiving a low daily maintenance dose of budesonide/formoterol (bud/form), replacing short-acting β_2-agonist (SABA) reliever therapy with the as-needed bud/form combination would enable patients to adjust more rapidly their antiinflammatory therapy at times of greatest need while simultaneously obtaining effective and rapid relief from symptoms. This approach should, therefore, further reduce asthma exacerbations and improve asthma control compared with the improvements seen with traditional fixed-dose combination therapy. Thus, this randomized, double-blind, 1-year study compared bud/form both for maintenance and symptom relief with fixed dosing using either bud/form or a fourfold higher dose of budesonide, both with SABA as reliever therapy. Previously, in the FACET study (2), which demonstrated that both budesonide and formoterol had complementary effects on reducing exacerbations in adults, a fourfold higher budesonide dose was more effective at reducing severe asthma exacerbations when compared with a low-dose bud/form combination, despite the combination providing greater improvements in symptoms (2). In this study, severe asthma exacerbations were selected as the primary outcome variable, as these are a sensitive clinical measure of control, responding to higher maintenance doses of budesonide, and thus are less likely to respond to low-dose combination therapy (2). Some of the results from this study have previously been presented in abstract form (8, 9).

METHODS

Patients

Outpatients aged 4 to 80 years with asthma treated with 400 to 1,000 μg/day of ICS for adults and 200 to 500 μg/day for children (4–11 years) with a history of one or more asthma exacerbation in the last year were enrolled. All patients had been using a constant dose of ICS for 3 or more months. Patients had an FEV_1 60–100% of predicted with 12% or more reversibility. To be eligible for randomization, patients had to have used 12 or more inhalations (or eight or more in children) of as-needed medication during the last 10 days of run-in. Patients using 10 or more inhalations of reliever on any 1 day (or seven or more for children) or with an asthma exacerbation during run-in were not randomized.

(Received in original form July 8, 2004; accepted in final form October 18, 2004)

Supported by AstraZeneca R&D, Lund, Sweden.

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This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org

Am J Respir Crit Care Med Vol 171. pp 129–136, 2005
Originally Published in Press as DOI: 10.1164/rccm.200407-884OC on October 22, 2004
Internet address: www.atsjournals.org

The study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Approval from regulatory agencies and ethics committees was obtained at all centers. All patients gave written informed consent.

Study Design

This was a double-blind, randomized, parallel-group study conducted at 246 centers in 22 countries. Patients attended the clinic at the beginning and end of run-in and after 1, 3, 6, 9, and 12 months of treatment.

Patients were randomized to one of three treatment groups: bud/form 80/4.5 μg twice a day plus 80/4.5 μg as needed (bud/form maintenance + relief), bud/form 80/4.5 μg twice a day plus terbutaline 0.4 mg as needed (bud/form + SABA), and budesonide 320 μg twice a day plus terbutaline 0.4 mg as needed (bud + SABA). Children were given half the maintenance dose once daily at night. Treatment was stratified by age group in an 8:1 ratio (adults:children), with all medication delivered by Turbuhaler (AstraZeneca, Lund, Sweden).

Adults could use a maximum of 10 and children 7 as-needed inhalations per day before contacting the investigator. Severe exacerbations were treated with a 10-day course of oral prednisone (30 mg/day); for children aged 4 to 11 years, the option to add extra maintenance medication during exacerbations was also available.

Measurements

Severe asthma exacerbations were defined as a deterioration in asthma resulting in hospitalization/emergency room treatment, oral steroid treatment (or an increase in ICS [via a separate inhaler] and/or other additional treatment for children aged 4–11 years), or morning peak expiratory flow (PEF) of 70% or less of baseline on 2 consecutive days. Severe exacerbations confined to those requiring medical intervention were also analyzed separately. Mild exacerbations were defined as 2 consecutive days with either a morning PEF of 80% or less of baseline, as-needed use two or more inhalation per day above baseline, or awakenings caused by asthma.

Daily pretreatment PEF was assessed using a Mini-Wright PEF meter (Clement Clark, Harlow, UK); daily symptoms, awakenings, reliever medication use, and study drug use were recorded on diary cards. FEV_1 was assessed by spirometry (10) at clinic visits. Safety was assessed by adverse events, electrocardiogram, morning plasma cortisol, and vital signs. Height for children aged 4 to 11 years was measured using local procedures before run-in and after 6 and 12 months of treatment.

Statistical Analysis

Data were analyzed on an intention-to-treat basis for patients who received one dose or more of study drug. All hypothesis testing was two sided; p values of less than 5% were considered statistically significant. The primary efficacy outcome was the time to first severe asthma exacerbation, described using Kaplan-Meier plots and a log-rank test, with analysis of instantaneous risk described using a Cox proportional hazards model. Total numbers of severe exacerbations were compared using a Poisson regression model. Confidence limits and p values were adjusted for overdispersion. The sample size was based on the true incidence of asthma exacerbations in one group being 25%. Therefore, a sample size of 800 randomized patients per group (i.e., 200 exacerbations) would provide an 80% probability of detecting a reduction of more than 23% in another group.

Other daily diary card variables were analyzed as change from baseline using analysis of variance, with the baseline value (last 10 days of run-in) as covariate. Individual growth was calculated as change in height between enrollment and after 12 months' treatment. Growth was compared between treatments using analysis of variance, with height at enrollment as a covariate. Further information on the study design and data analysis is provided in the online supplement.

RESULTS

Patients

In total, 3,251 patients were enrolled. After run-in, 2,760 patients were randomized to study treatment: 925, 909, and 926 patients to bud/form maintenance + relief, bud/form + SABA, and bud + SABA, respectively (Figure E1 in the online supplement). There were 437 patients (16%) with one or more protocol deviation, with no differences between groups. The most common deviation was randomization in error (9%), with the majority of these patients failing to meet the criterion for as-needed medication use during the run-in. None of the deviations justified exclusion of data from the analysis and all data were included where available. Of the 2,760 patients randomized, 341 (12%) were children aged 4 to 11 years. Characteristics of the treatment groups were comparable at baseline (Table 1).

Self-reported compliance with maintenance therapy was similar in all groups, with incomplete records on 12 to 13% of days/year, self-reported compliance on 84 to 85% of days/year, and noncompliance reported on 3% of days.

Severe Exacerbations

Bud/form maintenance + relief significantly prolonged the time to first severe exacerbation when compared with bud/form + SABA and bud + SABA (both $p < 0.001$) (Figure 1A). The risk of experiencing a severe asthma exacerbation was 45% lower when bud/form was used for maintenance and relief versus bud/form + SABA (hazard ratio [HR], 0.55; 95% confidence interval [CI], 0.44, 0.67) and 47% lower than a fourfold higher maintenance dose of bud + SABA (HR, 0.53; 95% CI, 0.43, 0.65). Some of the asthma exacerbations in all groups were a result of a fall in PEF (Figure 1B). These were mainly discovered on retrospective analysis of diary card data and did not result in medical intervention in 87% of cases. When these PEF falls were removed and only severe exacerbations requiring medical intervention were assessed, there was still a 50% reduction in the risk of experiencing a severe asthma exacerbation requiring medical intervention with bud/form maintenance + relief compared with bud/form + SABA (HR, 0.50; 95% CI, 0.40, 0.64) and a 45% reduction compared with bud + SABA (HR, 0.55; 95% CI, 0.43, 0.70). Bud/form maintenance + relief was also shown to prolong significantly the time to all exacerbations, including repeats ($p < 0.001$ compared with both alternative regimens) (Figure 2). This highly significant reduction in severe exacerbations was consistent in children, adolescents, and adults.

The relative rate of all types of severe exacerbations/patient was lowered by 47% in patients using bud/form for maintenance and relief compared with patients using either bud/form for maintenance only (HR, 0.53; 95% CI, 0.44, 0.65) or higher dose budesonide for maintenance (HR, 0.53; 95% CI, 0.44, 0.64). The rate of severe exacerbations requiring medical intervention was also reduced by 53% for bud/form for maintenance + relief compared with bud/form for maintenance only (HR, 0.47; 95% CI, 0.39, 0.57) and by 46% compared with higher-dose maintenance therapy with budesonide (HR, 0.54; 95% CI, 0.44, 0.66). The effect of using bud/form for maintenance and relief on exacerbation risk remained constant over time (Figure 2). In addition, bud/form maintenance + relief reduced the overall burden of severe exacerbations requiring medical intervention, decreasing first and repeated events by 134 and 170 events compared with bud + SABA and bud/form +SABA, respectively (Figure E2).

Mild Exacerbations

Patients in the bud/form maintenance + relief group had a significantly longer time to first mild exacerbation compared with those in the bud/form + SABA and bud + SABA groups (both $p < 0.001$). In addition, the rate (exacerbation days/subject) was 30% lower for bud/form maintenance + relief compared with bud/form + SABA (HR, 0.70; 95% CI, 0.62, 0.80) and 36% lower compared with bud + SABA (HR, 0.64; 95% CI, 0.57, 0.73).

TABLE 1. PATIENTS' BASELINE CHARACTERISTICS

Characteristic	Bud + SABA (*n* = 926)	Bud/form + SABA (*n* = 909)	Bud/form Maintenance + Relief (*n* = 925)
Male/female, n	416/510	394/515	421/504
Age, yr	36 (4–79)	36 (4–79)	35 (4–77)
4–11 years, n (%)	106 (11)	117 (13)	118 (13)
Asthma duration, yr	9 (0–69)	9 (0–65)	9 (0–63)
FEV_1, L	2.14 (0.64–4.02)	2.10 (0.62–4.50)	2.13 (0.65–4.28)
FEV_1, % predicted normal	73 (49–100)	73 (46–108)	73 (43–108)
FEV_1 reversibility, %	21 (3–77)	21 (12–75)	21 (2–89)
ICS dose at entry,* μg/day	620 (100–1000)	598 (200–1,000)	619 (200–1,200)
Inhaled LABA use at study entry†	256 (28)	258 (29)	250 (27)
Reliever use, number of inhalations/day	1.69 (0.0–7.0)	1.69 (0.0–9.4)	1.74 (0.0–8.0)
Reliever use, number of inhalations/night	0.72 (0.0–3.7)	0.73 (0.0–6.6)	0.72 (0.0–5.7)
Asthma symptom score (scale 0–6)	1.5 (0.0–5.6)	1.4 (0.0–5.2)	1.5 (0.0–6.0)
Symptom-free days, %	23.5 (0–100)	24.0 (0–100)	23.1 (0–100)
Reliever-free days, %	8.8 (0–100)	8.3 (0–100)	8.2 (0–100)
Asthma control days, %	5.6 (0–90)	5.9 (0–80)	5.4 (0–90)
Awakenings, % of nights	20.6 (0–100)	20.2 (0–100)	21.8 (0–100)

Definition of abbreviations: Bud = budesonide; form = formoterol; ICS = inhaled corticosteroids; LABA = long-acting β_2-agonist; SABA = short-acting β_2-agonist.

All values are presented as absolute numbers or as mean (range), except asthma duration (median).

*Values are a combination of metered and delivered doses.

† Includes combinations of ICS/LABA and LABA.

Study Drug Use

The mean number of daytime or nighttime inhalations of reliever medication was significantly lower for patients using bud/form maintenance + relief than for either comparator using SABA for relief (all $p < 0.001$; Table 2 and Figure 3A). On the majority of days (≥ 54%) patients remained reliever free in both the bud/form maintenance + relief group and in the bud/form + SABA group (Table 2). The mean daily budesonide dose used by adults and children is shown in Figure 4.

There were 495 episodes with an increase in as-needed medication to more than four inhalations per day over the baseline value in the bud/form maintenance + relief group, of which 37 were associated with an exacerbation; 1,347 episodes in the bud/form + SABA group, with 120 associated with an exacerbation; and 1,196 episodes in the bud + SABA group, with 96 associated with an exacerbation.

There were 26, 142, and 161 episodes of increased as-needed use of more than eight inhalations per day above baseline in the bud/form maintenance + relief, bud/form + SABA, and bud + SABA groups, respectively; of these, only 2 preceded an exacerbation in the bud/form maintenance + relief group compared with 17 and 23 in the bud/form + SABA and bud + SABA groups, respectively. The distribution of average daily as-needed medication use is shown in Figure E3. Patients using bud/form for maintenance and relief also had fewer courses of oral steroids, 0.19 courses per year for patients aged 12 to 80 years and 0.05 courses/year for children 4 to 11 years compared with patients receiving bud/form + SABA (0.42 and 0.30 courses per year for patients aged 12–80 and 4–11 years, respectively) and bud + SABA (0.38 and 0.25 courses per year for patients aged 12–80 and 4–11 years, respectively) (descriptive statistics only).

Symptoms

All treatments improved both asthma symptoms, as seen by a reduced requirement for reliever treatment, and awakenings from run-in (Figure 3B). Nighttime symptoms and awakenings were significantly improved in patients using bud/form for maintenance + relief compared with those using bud/form + SABA or a fourfold higher maintenance dose of bud + SABA (all $p <$ 0.05; Table 2). Based on adjusted means, the improved symptom control with bud/form for maintenance + relief resulted in an extra 14 nights per year free from awakenings compared with both alternative regimens. Bud/form + SABA significantly improved daytime and nighttime symptoms ($p < 0.05$) and asthma control days ($p < 0.001$) compared with a fourfold higher maintenance dose of bud + SABA; however, awakenings were similar for both groups. In contrast, all symptoms were improved with bud/form for maintenance + relief compared with a fourfold higher maintenance dose of bud + SABA (Table 2).

Lung Function

Morning PEF was improved from baseline in all treatment groups (Figure 3C). Bud/form for maintenance + relief significantly improved morning and evening PEF and FEV_1 compared with bud/form + SABA and bud + SABA (all $p < 0.001$; Table 2). In addition, bud/form + SABA significantly improved both morning and evening PEF compared with bud + SABA.

Safety

All treatments were well tolerated, and adverse events were generally mild to moderate in intensity. There were no notable differences between the three groups for adverse events or adverse events related to treatment with β_2-agonists or ICS (Table 3). The total number of patients with one or more adverse event was 528 (57%) with bud + SABA, 475 (52%) with bud/form + SABA, and 496 (54%) with bud/form for maintenance + relief. The number of patients with one or more serious adverse event was similar in each of the treatment groups: 5% (48/925) for bud + SABA, 7% (62/906) for bud/form + SABA, and 5% (46/922) for bud/form maintenance + relief. There were 7, 15, and 14 discontinuations because of respiratory events in the bud/form maintenance + relief, bud/form + SABA, and bud + SABA groups, respectively. Of these, aggravated asthma (worsening asthma) occurred in 2 patients in the bud/form maintenance + relief group compared with 13 and 8 patients in the bud/form + SABA and bud + SABA groups, respectively. There were one, two, and three cardiovascular events leading to discontinuation (general cardiovascular disorders, heart rate, and rhythm disorders, and myocardial, endocardial, and pericardial

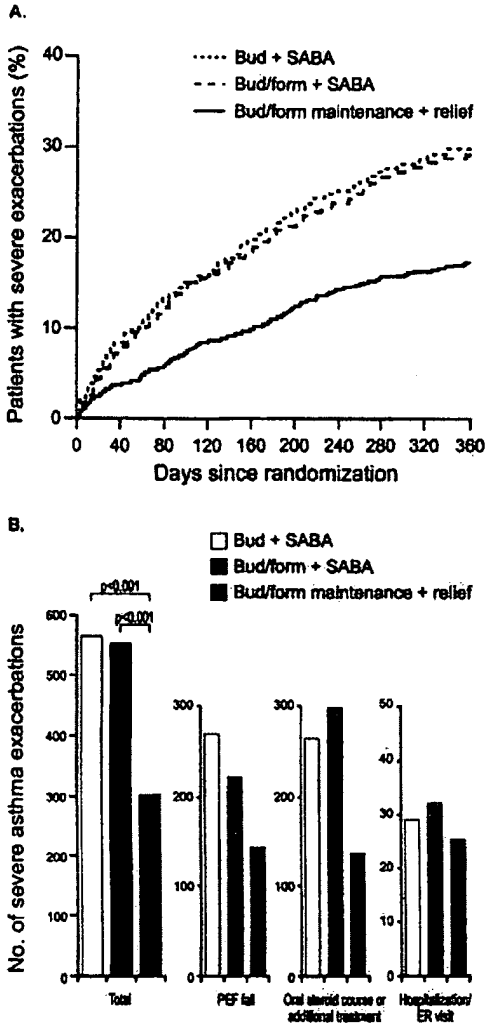

Figure 1. (*A*) Time to first severe exacerbation (deterioration in asthma resulting in morning peak expiratory flow [PEF] of 70% or less of baseline on 2 consecutive days; hospitalization/emergency room [ER] visit; treatment with oral steroids; or an increase in inhaled corticosteroids [ICS; via a separate inhaler] and/or other additional treatment as an additional criterion for patients aged 4–11 years). Bud/form maintenance + relief significantly prolonged the time to first severe exacerbation ($p < 0.001$ compared with both alternative regimens; Cox proportional hazards model). (*B*) Total number of severe asthma exacerbations and exacerbation subtypes (PEF fall, oral steroid course or additional treatment, hospitalization/ER visit). The p values are based on relative rate analysis (Poisson regression). Patients received 12 months of treatment with budesonide/formoterol (bud/form) 80/4.5 μg plus additional inhalations as needed (bud/form maintenance + relief), bud/form 80/4.5 μg plus terbutaline 0.4 mg (bud/form + short-acting β_2-agonist [SABA]), or budesonide 320 μg plus terbutaline 0.4 mg (bud + SABA). All maintenance treatments were twice daily for patients aged 12–80 years and once daily for children aged 4–11 years.

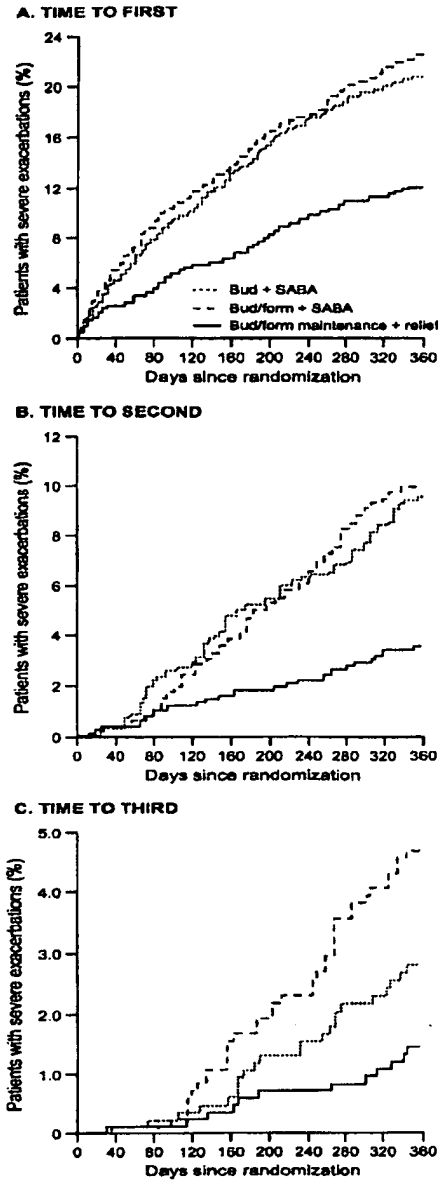

Figure 2. Kaplan-Meier plot of time to severe asthma exacerbation (defined as a deterioration in asthma resulting in hospitalization/ER visit; treatment with oral steroids and/or an increase in ICS [via a separate inhaler] and/or other additional treatment as an additional criterion for patients aged 4–11 years). (*A*) Time to first exacerbation. (*B*) Time to second. (C) Time to third. Patients received 12 months of treatment with bud/form 80/4.5 μg plus additional inhalations as needed (bud/form maintenance + relief), bud/form 80/4.5 μg plus terbutaline 0.4 mg (bud/form + SABA), or budesonide 320 μg plus terbutaline 0.4 mg (bud + SABA). All maintenance treatments were twice daily for patients aged 12–80 years and once daily for children aged 4–11 years. Bud/form maintenance + relief significantly prolonged the time to all exacerbations, including repeats ($p < 0.001$ compared with both alternative regimens; Cox proportional hazards model).

disorders and valve disorders) in the bud/form maintenance + relief, bud/form + SABA, and bud + SABA groups, respectively. Other events led to 11, 23, and 13 discontinuations, respectively.

No clinically important differences in electrocardiogram, hematology, clinical chemistry, or urinalysis were observed between treatment groups or over time. In subgroups of patients aged 12–80 and 4–11 years in whom plasma cortisol was assessed, there were no significant findings (*see* Table E1).

Children (4–11 years) in both bud/form groups grew significantly more than those in the bud + SABA group. There was an

TABLE 2. CLINICAL OUTCOMES

Variable	Bud + SABA	Bud/form + SABA	Bud/form Maintenance + Relief	p Values: Bud/form + SABA vs. Bud + SABA	p Values: Bud/form Maintenance + Relief vs. Bud + SABA	p Values: Bud/form Maintenance + Relief vs. Bud/form + SABA
Severe exacerbations including PEF falls						
Patients with event, %*	28	27	16	0.74	< 0.001	< 0.001
Events/patient/year†	0.68	0.68	0.36	0.98	< 0.001	< 0.001
Severe exacerbations resulting in medical intervention						
Patients with event, %*	19	21	11	0.37	< 0.001	< 0.001
Events/patient/year†	0.35	0.40	0.19	0.11	< 0.001	< 0.001
Daily control measures						
Daytime symptom score‡	0.59	0.50	0.48	< 0.001	< 0.001	0.12
Night-time symptom score‡	0.42	0.36	0.31	0.01	< 0.001	< 0.001
Reliever use, inhs/day	1.03	0.84	0.73	< 0.001	< 0.001	< 0.001
Reliever use, inhs/night	0.43	0.37	0.28	0.003	< 0.001	< 0.001
Symptom-free days, %	46	53	54	< 0.001	< 0.001	0.52
Reliever-free days, %	45	54	55	< 0.001	< 0.001	0.60
Asthma control days, %§	37	44	45	< 0.001	< 0.001	0.64
Awakenings, % of nights	12	12	9	0.60	< 0.001	< 0.001
Mild exacerbation days, %¶	20	23	17	0.06	0.03	< 0.001
Morning PEF, L/min	339	346	355	< 0.001	< 0.001	< 0.001
Evening PEF, L/min	345	349	360	< 0.001	< 0.001	< 0.001
FEV_1, L	2.41	2.43	2.51	0.09	< 0.001	< 0.001

Definition of abbreviations: Bud = budesonide; form = formoterol; inhs = inhalations; PEF = peak expiratory flow; SABA = short-acting β_2-agonist.

Daily control measures are mean values over 12 months of treatment.

* p Values based on the instantaneous risk of experiencing at least one severe exacerbation (Cox proportional hazard model).

† p Values based on relative rate analysis (Poisson regression).

‡ Symptoms were scored from 0 (no asthma symptoms) to 3 (unable to undertake normal activities [or to sleep] because of symptoms).

§ Asthma control days were defined as a day with no symptoms (day or night), no awakenings caused by asthma, and no as-needed medication use.

¶ Mild exacerbation days (periods with worsenings) were defined as any day with an awakening caused by asthma, or with as-needed medication use of two or more inhalations above the baseline mean value or with morning PEF of 80% or less of baseline mean value.

adjusted mean difference in growth of 1.0 cm between children treated with bud/form for maintenance + relief versus bud + SABA (95% CI, 0.3, 1.7; p = 0.0054) and a difference of 0.9 cm between bud/form + SABA versus bud + SABA (95% CI, 0.2, 1.6; p = 0.0099).

DISCUSSION

This study examined the hypothesis that bud/form used for regular maintenance therapy and symptom relief would further reduce exacerbations and improve overall asthma control compared with traditional ICS/LABA therapy. ICS plus LABA has demonstrated efficacy in adults with asthma (1, 2) and is recommended by guidelines as the optimal therapy for patients with moderate to severe asthma (4). The study demonstrated that bud/form for maintenance and relief significantly reduced total severe exacerbations, severe exacerbations requiring medication intervention, and exposure to oral steroids, as well as reducing reliever medication use, night-time symptoms including awakenings, and mild exacerbation days and improving lung function when compared with either bud/form or a fourfold higher dose of budesonide for maintenance therapy, both with SABA for relief.

The asthma management approach used in this study is an evolution of the ICS plus LABA approach demonstrated to be effective in the OPTIMA (1) and FACET (2) studies. These studies showed that exacerbations were less common in the majority of patients treated with the addition of LABA to ICS compared with those receiving a twofold or fourfold higher dose of ICS. The only notable benefit of the fourfold higher dose of budesonide in the FACET study was to prevent repeated severe exacerbations. This study is the first to show that a high-maintenance dose of budesonide is not necessary to reduce the incidence of first and repeated severe exacerbations requiring medical intervention. The risk of a severe exacerbation requiring medical intervention was reduced by 45% with bud/form for maintenance and relief compared with patients using a fourfold higher maintenance dose of budesonide with SABA for relief. Moreover, the time to second and third exacerbations was significantly prolonged with bud/form for maintenance and relief compared with the fourfold higher maintenance dose of budesonide with SABA. This suggests that bud/form for maintenance and relief is also effective in patients with more severe asthma who experience repeat exacerbations.

The magnitude of the benefits achieved in this study with bud/form for maintenance and relief (with a mean daily dose of budesonide of 240 μg/day in adults and 126 μg in children) when compared with a fourfold higher maintenance dose of budesonide (with a mean daily dose of 640 μg/day in adults and 320 μg/day in children) was surprising and suggests that it is the timing of the increase in ICS dose—resulting from as-needed use of bud/form in response to symptoms—rather than the total inhaled dose of ICS that improves efficacy. Studies that simply doubled the maintenance dose of ICS well into the course of an exacerbation have generally failed to show added benefits (11, 12). The evaluation by Tattersfield and colleagues (13) of all severe exacerbations that occurred in the FACET study suggests that there is a period of 5 to 7 days before a severe exacerbation is recognized and needs to be treated with oral corticosteroids, during which patients experience deteriorating symptoms and lung function. This represents an opportunity to intervene early with an increase in ICS. There is also evidence that as-needed use of formoterol has benefits for asthma control. Patients using as-needed formoterol in addition to regular maintenance therapy with an ICS or an ICS/LABA combination have fewer severe exacerbations than patients using terbutaline (14) or salbutamol

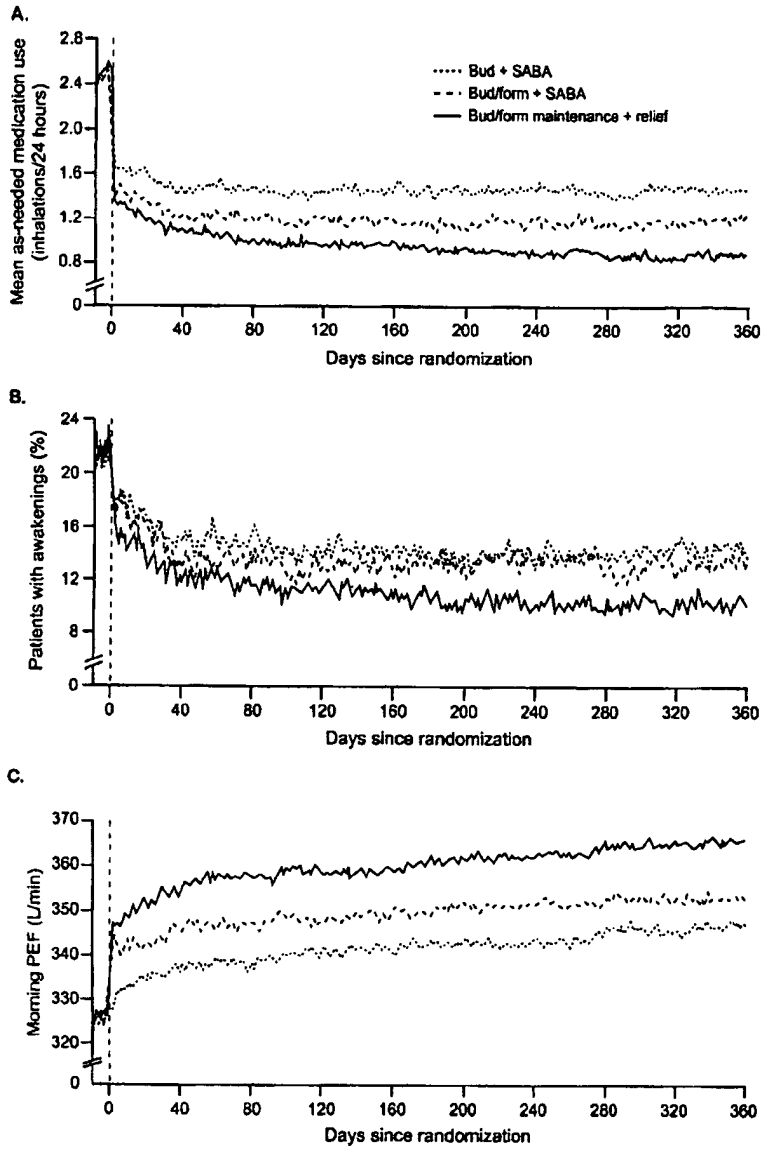

Figure 3. Diary card data showing change from run-in over the entire 12-month treatment period. (*A*) Mean reliever inhalations per 24 hours. (*B*) nights with awakenings because of asthma. (C) Morning PEF. Patients were randomized to 12 months of treatment with bud/form 80/4.5 μg plus additional inhalations as needed (bud/form maintenance + relief), bud/form 80/4.5 μg plus terbutaline 0.4 mg (bud/form + SABA), or budesonide 320 μg plus terbutaline 0.4 mg (bud + SABA). All treatments were twice daily for patients aged 12–80 years and once daily for children aged 4–11 years; $p < 0.001$ for bud/form maintenance + relief versus bud/form + SABA and bud + SABA for daily reliever use, nights with awakenings, and morning PEF (analysis of variance).

as needed (15). Furthermore, increasing both budesonide and formoterol provides greater protection from inflammatory challenges than increasing either agent alone (16).

Patients who do not adhere fully to ICS and instead overrely on SABAs as reliever medication are at increased risk of experiencing asthma exacerbations (17, 18). Bud/form for maintenance and relief reduces the potential for patients to overrely on their reliever medication (which, in the case of SABAs, do not treat underlying inflammation) and instead responds to symptoms with a combination of bud/form. This ensures that patients receive an immediate increase in antiinflammatory medication plus rapid and sustained symptom relief. Also, concerns that the use of the LABA alone may mask subclinical airway inflammation (19) are not an issue with bud/form for maintenance and relief, as ICSs are always delivered with reliever medication to control underlying inflammation. Importantly, there was no evidence of tolerance to medication in patients using bud/form for maintenance and relief, as improvements in exacerbation control, lung function, awakenings, and reliever-free days were maintained over the 12-month study period.

The fourfold higher maintenance dose of budesonide plus SABA may have been superior to the fixed-dose bud/form plus SABA treatment in controlling asthma exacerbations in the most severe patients, despite fixed-dose bud/form plus SABA providing superior improvements in lung function, reliever-free days, and asthma control days. Patients in the fourfold higher budesonide plus SABA group had fewer exacerbations requiring medical intervention, although this difference did not reach statistical significance. Although time to first exacerbation was similar in these two groups, time to a third exacerbation was prolonged to a greater extent by high-dose budesonide plus SABA treatment. This result is similar to the outcome of the FACET study (2), where patients with more severe asthma prone to frequent exacerbations benefited from a higher dose of ICS.

There was no evidence for overuse of reliever bud/form. On average, 55% of days were reliever use free in the bud/form maintenance plus relief group and the mean number of as-needed doses of bud/form was one additional dose per day. This amount of as-needed reliever use with fixed combination therapy

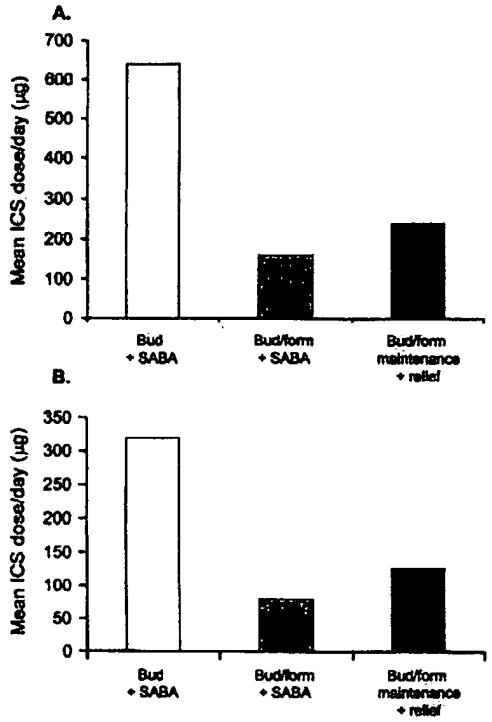

Figure 4. Mean daily ICS doses. (*A*) Patients aged 12–80 years. (*B*) patients aged 4–11 years. Patients were randomized to 12 months of treatment with bud/form 80/4.5 μg plus additional inhalations as needed (bud/form maintenance + relief), bud/form 80/4.5 μg plus terbutaline 0.4 mg (bud/form + SABA), or budesonide 320 μg plus terbutaline 0.4 mg (bud + SABA). All treatments were twice daily for patients aged 12–80 years and once daily for children aged 4–11 years.

(i.e., 50% of days with use or an average of one inhalation per day) has been a common finding in several studies of patients with moderate to severe asthma using salmeterol/fluticasone (20–22) and bud/form (22, 23). In addition, there were notably fewer episodes of high as-needed medication use, that is, at least eight inhalations above baseline, in the bud/form maintenance + relief group compared with the fixed dosing groups. Bud/form maintenance + relief was also associated with only 2 severe exacerbations in the high-user subgroup compared with 17–23 severe exacerbations in patients using terbutaline for reliever medication. The average daily dose of budesonide resulting from maintenance and relief use of bud/form was 80 μg higher than for patients who used bud/form for fixed maintenance only (bud/form + SABA group). Importantly, no additional drug-related adverse events were identified with the use of extra bud/form for relief in addition to maintenance.

Asthma treatment guidelines (4) advocate a stepwise approach to asthma management. bud/form for maintenance and relief mirrors this recommendation. Patients step up their controller medication by using bud/form for relief of breakthrough symptoms. Adjustments in medication occur from the first onset of symptoms, however, rather than after a medication review. Once control is regained, patients step down treatment by using bud/form for daily maintenance treatment only, without additional as-needed inhalations.

In conclusion, using bud/form for both maintenance and relief reduces the risk and rate of severe asthma exacerbations and the need for systemic steroids and improves asthma symptoms, nocturnal awakenings, and lung function compared with traditional fixed dosing regimens, therefore reducing the morbidity and potentially the mortality of asthma.

Conflict of Interest Statement: P.M.O. is a consultant and sits on advisory boards for AstraZeneca, Altan, GlaxoSmithKline (GSK), Topigen, Bristol-Myers Squibb (BMS) Roche, and Merck and has also been a paid lecturer for these companies and holds sponsored grants from Altana, AstraZeneca, Dynavax, GSK, Ono, and Merck and does not hold stock or options in any pharmaceutical company; H.B. has within the last 3 years received honoraria for lectures and attendance at pediatric Advisory Boards for Aerocrine, AstraZeneca, GSK, Hoffman La Roche, Merck, Novartis, and Yamanouchi and holds no stock options in pharmaceutical industry in the respiratory field and owns a world patent for an inhaler device but receives no royalty, and the COPSAC clinical research unit has in the last 3 years received research grants from the following industry partners in increasing order: Aerocrine, Merck, GSK, and AstraZeneca; P.P.C. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; M. Pistolesi received a grant from AstraZeneca £51,000 to perform the STAY study; M. Palmqvist does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; Y.Z. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; T.E. is an employee of AstraZeneca Sweden since 1997 with special reference to the clinical development of the fixed combination of bud/form and has stock options in the company and a pending patent on the as needed use of bud/form in asthma and also chairs yearly national advisory boards in respiratory medicine; E.D.B. has received honoraria for speaking at scientific meetings and courses organized and financed by AstraZeneca, Boehringer Ingelheim, and GSK and has served on advisory boards for AstraZeneca, Boehringer Ingelheim, Hoffman le Roche, and GSK.

TABLE 3. COMMON ADVERSE EVENTS BY TYPE (≥ 5% INCIDENCE) AND ANY PHARMACOLOGICALLY PREDICTABLE ADVERSE EVENTS

	Number of Patients (%)		
	Bud + SABA (*n* = 925)	Bud/form + SABA (*n* = 906)	Bud/form Maintenance + Relief (*n* = 922)
Respiratory infection	182 (20)	144 (16)	158 (17)
Pharyngitis	86 (9)	88 (10)	88 (10)
Rhinitis	76 (8)	72 (8)	80 (9)
Bronchitis	76 (8)	61 (7)	51 (6)
Sinusitis	33 (4)	39 (4)	43 (5)
Headache	42 (5)	35 (4)	31 (3)
Pharmacologically predictable events			
Tremor	19 (2)	18 (2)	20 (2)
Palpitation	3 (< 0.5)	11 (1)	10 (1)
Tachycardia	3 (< 0.5)	4 (< 0.5)	5 (0.5)
Candidiasis	10 (1)	6 (1)	9 (1)
Dysphonia	12 (1)	13 (1)	11 (1)

Definition of abbreviations: Bud = budesonide; form = formoterol; SABA = short-acting β_2-agonist.

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A Single Inhaler for Asthma?

Despite the availability of highly effective therapies, many patients with asthma continue to suffer symptoms and exacerbations, with considerable disruption to their daily life (1). This may reflect underdiagnosis and inappropriate therapy, as well as poor adherence to regular prophylactic therapy. Inhaled corticosteroids are the mainstay of asthma therapy, but there is now compelling evidence that addition of a long-acting inhaled β_2-agonist (LABA: salmeterol or formoterol) gives better control in terms of reduced symptoms, improved lung function, and reduced exacerbations in patients with mild, moderate, and persistent asthma (2–4). This has led to the development of fixed combination inhalers (salmeterol/fluticasone, formoterol/budesonide), which are now increasingly used in asthma management (5, 6).

Combination inhalers are more convenient to use, control asthma at lower doses of corticosteroids, ensure that the corticosteroid is not discontinued when the bronchodilator is used, and are cost effective. There is a convincing scientific rationale for giving an LABA and corticosteroid together, as they have complementary actions on the complex pathophysiology of asthma and may enhance each other's effects at a molecular level (7). It is normal practice to administer these combination inhalers twice daily at a dose that is related to the severity of asthma and to use a short-acting β_2-agonist (SABA), such as albuterol, as required to relieve any breakthrough symptoms. Frequent use of the SABA indicates either poor compliance or the need for a higher maintenance dose of the combination inhaler. A recently published large study (over 3,000 patients) attempted to achieve better, and if possible total, control of asthma by progressively increasing the dose of the controller inhaler (8). Control was more easily and rapidly achieved with the salmeterol/fluticasone combination inhaler than fluticasone alone and at a lower total dose of inhaled corticosteroid. However, some patients required rather high doses of the combination inhaler to achieve satisfactory control of their asthma.

This issue of the *Journal* (pp. 129–136) presents a new study that takes this approach a step further (9). It had previously been shown that formoterol could be used as a reliever medication in asthma, as it has a rapid onset of action with a long bronchodilator effect, yet systemic side effects are of a similar duration to an SABA (10). In the new double-blind controlled parallel group study (involving over 2,500 patients) formoterol/budesonide combination inhaler was used as maintenance therapy twice daily, but additional puffs were used as needed for symptom relief (9). This was compared with the same maintenance dose and to a fourfold greater dose of budesonide alone, both with terbutaline as needed. The remarkable, and somewhat unexpected, finding was that the treatment with combination inhaler for both maintenance and relief markedly reduced the number of severe exacerbations (the primary outcome measure) over the 1-year treatment period compared with the other treatments, but also reduced the need for oral corticosteroids, improved symptom control, and lung function compared with the other treatment regimens. A concern about this approach is that some patients might end up using the combination inhaler frequently and therefore receive an unacceptably high dose of inhaled corticosteroid. However, this was not the case, as the mean number of additional doses of combination inhaler was only one dose per day and very few patients used high doses. Combination inhalers have generally been less effective in children with asthma (11), as LABA do not appear to have such a large add-on effect. In this study, children aged 4–11 years (12% of study population) were also included, but there is no information provided on how they responded to the different treatment strategies compared with adults.

How can these surprisingly good results be explained mechanistically? Asthma is characterized by variable symptoms with day-to-day variability. One approach to deal with such variability is by giving a high dose of combination inhaler to prevent the emergence of symptoms, as adopted by the salmeterol/fluticasone study (8). An alternative approach is to increase the treatment at the time asthma worsens. We know from the careful analysis of asthma exacerbations in a large controlled trial that they evolve slowly over a few days (12). This provides the opportunity to intervene before the exacerbation develops fully. It is now clear that doubling the maintenance dose of inhaled corticosteroid is insufficient to prevent an exacerbation (13), whereas a fourfold increase is effective (2), and confirmed by the present study. It is likely that the combination inhaler not only provided an effective bronchodilator to relieve symptoms, but also a steroid at a time when it is needed. It is now emerging that inhaled corticosteroids work much more rapidly than previously recognized, with significant antiinflammatory and bronchoprotective effects detectable after a few hours (14, 15). The reason why the additional rescue treatment with the combination inhaler on top of the maintenance dose is so effective is presumably related to timing and its effect of "nipping in the bud" the evolution of an exacerbation. It is likely that the corticosteroid component is most important in this respect, although this needs to be demonstrated in a controlled trial using formoterol, rather than terbutaline, as the rescue therapy. It may, however, be the combination of the two drugs that is important, with some critical interaction between the LABA and the corticosteroid which enhances the effectiveness of this approach. Further research is now needed to understand the molecular mechanism involved and whether this approach more effectively controls airway inflammation.

The study by O'Byrne and colleagues may lead to changes in the paradigm of asthma management, where a single inhaler is used for both maintenance and rescue (9). This simplifies asthma therapy for the patients (and the doctor) and is likely to improve compliance. It also follows more closely what patients do in the real world, where they tend take more medication in response to increased symptoms. It is also likely that this treatment strategy will be more cost effective as better control of asthma reduces the costs of treating exacerbations and hospital admissions. We now need effectiveness studies in the real world to see whether this simplified approach is applicable to treating asthma patients in the community (16).

Am J Respir Crit Care Med Vol 171. pp 95–97, 2005
Internet address: www.atsjournals.org

Conflict of Interest Statement: P.J.B. has served on Scientific Advisory Boards, received lecture fees and research funding for GlaxoSmithKline, AstraZeneca, Boehringer-Ingelheim, Novartis, Altana, Pfizer, Scios, and Millennium.

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DOI: 10.1164/rccm.2410004

Therapeutic Hypercapnia: Careful Science, Better Trials

Reducing tidal volumes in patients with injured lungs—a strategy associated with elevated carbon dioxide—improves patient survival (1, 2). Laboratory studies have documented benefits of hypercapnia, as well as some mechanisms of action (3–5). Moreover, buffering hypercapnic acidosis attenuates its benefit, and hypocapnia can be harmful (6). All of the above suggests that hypercapnia might soon evolve into a testable clinical therapy (7).

In the current issue of the *Journal* (pp. 147–157), a paper from Lang and coworkers injects a dose of disquiet into this evolving carbon dioxide story (8). The authors have investigated an animal model of sepsis and found that their particular strategy of permissive hypercapnia increased—not decreased—lung inflammation (8). This article follows an earlier report of adverse effects of hypercapnia from the same group (9), multiple studies of its free radical biochemistry (10), and extensive experience at the bedside—particularly with pulmonary or intracranial hypertension.

So there are two sides to the hypercapnia story and a spectrum of interpretations. The current study is superficially at odds with several previous studies (5, 11–13), including some from our laboratory. The worst possible approach would be to ignore or condemn the new data because they do not fit with one's prior ideas. This would be anti-science. The appropriate approach is to review all the information carefully to understand it fully.

How then, do we learn from the current data? I see three questions and three lessons. First, are the findings of the current study attributable to hypercapnia, or to the means of achieving it? Lang and colleagues allocated animals to a strategy of "permissive hypercapnia" by lowering the respiratory rate, not the tidal volume (8). Of course, achieving "permissive hypercapnia" by reducing respiratory rate is unusual at the bedside. In fact, clinicians usually reduce tidal volume, and to compensate, increase the respiratory rate. This may be important, because low values of tidal volume, positive end-expiratory pressure, and respiratory rate may cause atelectasis. Indeed, it has been suggested that benefits associated with one low tidal volume strategy may actually be due to intrinsic positive end-expiratory pressure resulting from the increased respiratory rate (14). As well, the authors remind us that in contrast to adding inspired carbon dioxide, hypoventilation may result in uneven distribution of carbon dioxide throughout the lung (15). Indeed, "therapeutic hypercapnia," through raising the arterial carbon dioxide by increasing inspired concentration, is not frequently practiced in the clinical setting but has proved effective in the laboratory (5). Finally, the authors point out that the use of 100% inspired oxygen (8), a level avoided by most clinicians, might have exacerbated inflammatory events (16). Therefore, in answer to the first question, all hypercapnia may not be equal, and the differences may in part be due to other aspects of the ventilatory management.

Second, what do we learn about the complexity of hypercapnia? The current study expands our horizons regarding the pathogenic mechanisms associated with elevated levels of carbon dioxide which can alter the formation of peroxynitrite, and result in either "relatively protective" or "relatively injurious" intermediates. The authors discuss the recent study by Laffey and coworkers that demonstrated protection against endotoxin-induced lung injury with added carbon dioxide (11). Whereas that study suggested that the nitrotyrosine formation might represent a reservoir that could "mop up" the more toxic nitrate/nitrite intermediates in the lung (11), the current study demonstrated that inhaled nitric oxide decreased tissue injury (8), but without altering the formation of nitrotyrosine. Thus, in answer to the second question, inhaled nitric oxide may lessen lung injury associated with endotoxin and hypercapnia, and illustrates the lesson that nitrotyrosine formation might be more a marker of injury than a pathogen.

Third, what are the implications for rapid implementation at the bedside? There is an intense personal and professional desire within all of us to get results for patients—and quickly. This was

WHAT ARE THE SPECIFIC DRUGS USED TO PREVENT ASTHMA ATTACKS AND REDUCE AIRWAY INFLAMMATION?

Corticosteroids

Corticosteroids, also called glucocorticoids or steroids, are powerful anti-inflammatory drugs. Steroids are not bronchodilators (that is, they do not relax the airways) and hav little effect on symptoms. Instead, they work over time to reduce inflammation and prevent permanent injury in the lungs. Many studies have now shown that the use of inhaled corticosteroids in patients with moderate to severe asthma significantly reduce the rate of rehospitalizations and deaths from asthma. Nevertheless, they are still significantly underprescribed in the patients who need them most.

Inhaled Corticosteroids. Inhalation of corticosteroids makes it possible to provide effective local anti-inflammatory activity in the lungs with minimal systemic effects. (Or steroids have considerable side effects.) They are currently recommended as the primary therapy under the following circumstances:

- For any asthmatic condition more serious than occasional episodes of mild asthma. (Low-doses of inhaled steroids may even be safe and effective for som people with mild asthma, particularly those who find themselves using beta2-agonists daily.)
- When treatment with bronchodilators is not effective.

Examples of inhaled corticosteroids are the following:

- The most recent generation of inhaled steroids include (in order of potency) fluticasone (Flovent), budesonide (Pulmicort), triamcinolone (Azmacort and others), and flunisolide (AeroBid). In general, the newer agents, are more powerful than the older generation of inhaled agents. Experts have some concern, then, that these potent agents, particularly fluticasone, may produce major side effects similar to oral agents. Studies are now suggesting, however, that the same benefits can be achieved with low doses of fluticasone as with hi doses, thus reducing risks for serious side effects. (Of note, budesonide appea to be safe during pregnancy.)
- The older corticosteroid inhalants are beclomethasone (Beclovent, Vanceril) an dexamethasone (Decadron Phosphate Respihaler and others). They are less powerful than the newer steroids when delivered with standard inhalers. New inhaler systems for, however, such as QVAR, which uses extra fine formulation of beclomethasone to allow deep delivery into the lungs may prove to be as effective as the newer, more potent steroids.
- Inhalers that combine both long-acting beta2-agonists and corticosteroids are now available. [*See* Combinations of Corticosteroids and Long-Acting Beta2 Agonists.]

Budesonide Inhaler

Printable Version

Active Ingredients: Budesonide Inhaler
Representative Names: Pulmicort
Available Product Images:

What is budesonide inhalation powder? (Back to top)

BUDESONIDE (Pulmicort Turbuhaler®) is a corticosteroid for treating respiratory problems. It helps to decrease the inflammation, swelling, and irritation in your lungs that is caused by asthma or other lung diseases. Regular use of budesonide inhalation powder will help prevent asthma attacks, but it is not for rapid relief of asthma attacks. Generic budesonide inhalation powder is not yet available.

What should my health care professional know before I use budesonide? (Back to top)

They need to know if you have any of these conditions:
•Cushing's syndrome
•infection such as herpes, or tuberculosis
•recent surgery or trauma
•an unusual or allergic reaction to budesonide, steroids, other medicines, foods, dyes, or preservatives
•pregnant or trying to get pregnant
•breast-feeding

How should I use this medicine? (Back to top)

Budesonide is for inhalation through the mouth. Follow the directions on the prescription label. A new inhaler should be primed before use. Follow the priming instructions that come with the inhaler. The instructions will also tell you what position to hold the inhaler when loading or inhaling a dose. Always hold the inhaler in the appropriate position so that no medication is lost.

Load the dose as instructed. Do not shake the inhaler after loading it. Turn your head away from the inhaler and breathe out. Place the mouthpiece between your lips and inhale deeply and forcefully. You may not taste or feel the medication. Remove the inhaler from your mouth and exhale. Do not blow or exhale into the mouthpiece. Do not chew or bite on the mouthpiece. If more than one dose is required, repeat the steps above. Rinse your mouth with water; do not swallow the water.

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budesonide inhalation

Pronunciation: bew DEH so nide
Brand: Pulmicort Respules, Pulmicort Turbuhaler

What is the most important information I should know about budesonide inhalation?

- Budesonide inhalation will not stop an asthma attack that has already started. It is used to prevent attacks.
- Do not use more of this medication than is prescribed for you. Too much may cause serious side effects.
- Use budesonide inhalation on a regular basis for best results. It may take several weeks to get the maximum effect of this medication.
- It is very important that you use your budesonide inhaler or nebulizer properly, so that the medicine gets into your lungs. Talk to your doctor about proper inhaler or nebulizer use.
- Seek medical attention if you notice that you require more than your usual or more than the maximum amount of any asthma medication in a 24-hour period. An increased need for medication could be an early sign of a serious asthma attack.

What is budesonide inhalation?

- Budesonide is a steroid. It prevents the release of substances in the body that cause inflammation.
- Budesonide inhalation is used to prevent asthma attacks.
- Budesonide may also be used for purposes other than those listed in this medication guide.

Who should not use budesonide inhalation?

- Before using budesonide inhalation, tell your doctor if you have a viral, bacterial, or fungal infection of any kind. The absorption of this drug into your system can inhibit your body's ability to fight off infections. You may not be able to use budesonide inhalation if you have an infection.
- Budesonide inhalation will not stop an asthma attack that has already started. It is used to prevent attacks. Do not use budesonide inhalation to treat an asthma attack. If you are having an asthma attack that is not responding to any treatment, seek emergency medical attention.
- Budesonide inhalation is in the FDA pregnancy B. This means that it is not expected to harm an unborn baby. Do not use this medication without first talking to your doctor if you are pregnant.
- It is not known whether budesonide passes into breast milk. Do not use budesonide inhalation without first talking to your doctor if you are breast-feeding a baby.

How should I use budesonide inhalation?

- Use budesonide inhalation exactly as directed by your doctor. Read the information insert included with your inhaler. If you do not understand these directions, ask your pharmacist,

(x) Related Proceedings Appendix

None.